Non-additive effects of age, MCI and *APOE* on measures of the Attentional Reorienting System

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Main thesis – Department of Psychology

UNIVERSITETET I OSLO

29.04.2011

2011

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Trykk: Reprosentralen, Universitetet i Oslo

Abstract

The current study investigates effects of normal aging, subjective/mild cognitive impairment (SCI/MCI) and apolipoprotein E gene (*APOE*) on different aspects of cognitive control. Cognitive control tasks were believed to be sensitive to distinguish normal aging vs. prodromal Alzheimer's disease (AD) processes. 679 healthy participants aged 18-79 (M = 48.2, SD = 18, Male/Female = 462/217), and 66 patients with diagnosis SCI/MCI aged 46-77 (M = 60.7, SD = 6.8, Male/Female = 34/32) were recruited, screened for exclusion criteria, tested on psychometric tests (Stroop, Matrix Reasoning, Digit Symbol, Letter-Number Span, TMT A, TMT B) and three different neuropsychological experiments (1: covert visuospatial orienting task, 2: context processing/updating task, 3: visuospatial working memory). Based on previous findings, non-additive effects of MCI+*APOE* ε4 were expected only on measures that activate the *attentional reorienting system*, i.e. cost of invalid cues in experiment 1, and BX-trials in experiment 2. Separate ANOVAs in the analysis were conducted with Group (Young Control (YC) aged 18-45, Old Control (OC) aged 46-79, MCI, aged 46-77), and *APOE* (+ε4, ÷ε4) as between-subject factors, and different within-subject factors for all three experiments based on cognitive theory. Effects of normal age (OC ÷ YC) were contrasted to effects of MCI (MCI ÷ OC), and different patterns of results were revealed on different tests. On all psychometric tests a decline of normal aging was found, and MCI exacerbated the decline in an additive way, with no *APOE* involvements. On visuospatial working memory, a similar pattern was found, that is: MCI added to the decline of normal age, with no modulations of *APOE*. However, on predicted component measures in experiment 1 & 2, MCI patients showed a performances pattern that seemed to be different (non-additive) from normal age effects. These effects were modulated by *APOE* in the MCI group only, indicating that *APOE*ε4 played a specific role in pathological aging effects on these measures believed to activate the attentional reorienting system. The attentional reorienting system is activated by unexpected but behaviorally relevant targets, and modulated by both ventral and dorsal frontoparietal networks in the brain (Corbetta, Patel, & Shulman, 2008). It was discussed whether measures of the attentional reorienting system may be interpreted as a cognitive endophenotype, being an intermediate step in the *APOE*-AD link.

Acknowledgements

The data used in this thesis are part of a bigger project that started in 2003. Data acquisition was from 2004 – 2010. Partners in this project are: the Center for the Study of Human Cognition, Department of Psychology, University of Oslo, Oslo, Norway (involving Thomas Espeseth & Ivar Reinvang), the Department of Neurology, Akershus University Hospital, Lørenskog, Norway (involving Ramune Grambaite & Tormod Fladeby), the Department of Biological and Medical Psychology, Faculty of Psychology, University of Bergen, Bergen, Norway (involving Astri J. Lundervold), the Cognitive Genetics Group, Arch Lab, George Mason University, Fairfax, VA, USA (involving Pamela M. Greenwood & Raja Parasuraman), and Department of Medical Biochemistry, Rikshospitalet University Hospital, Oslo, Norway (involving Helge Rootwelt). I am grateful to Thomas Espeseth for support, assistance, and for the opportunity he gave me to participate in this project. Thanks to all participant I have met.

About my participation: I became involved in this project as a scientific trainee from September 2008 up till date, and have participated in recruiting procedures, screening, and test administration. Since I began working on this thesis several years after the project started, most of the experimental paradigms were already selected and implemented. The initial aim was to conduct an explorative study about how age, MCI and *APOE* affected systems of visuospatial attention and working memory. Part of my work was to select data that could be used for this. After I analyzed data on two experiments, and wrote my first draft, my supervisor Thomas Espeseth made me aware of the attentional reorienting system, and proposed the idea of including another experiment. The idea to follow a specific hypothesis intrigued me, as it made the work in this study more strict and content. My specific participations thereafter concerned discussions about which variables and results to focus on, how the hypothesis may be discussed by this selection of measures, and obviously, to write and structure the text, conduct statistical analysis and interpret all presented results. But, because this study was part of a bigger context, I narrated the hypothesis and predictions in first-person we-form.

Peter Strassegger

Oslo, April 2011.

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1 Introduction

1.1 Aging studies

Cognitive control is believed to increase in efficiency, speed and complexity from childhood to young adulthood, but then declines as people get older or become demented (Craik & Bialystok, 2006; Parasuraman & Haxby, 1993). Normal aging is often characterized by reduced function of frontal brain networks, affecting cognitive control functions, such as perceptual speed, working memory, selective attention or executive function (Buckner, 2004; Craik & Bialystok, 2006). Alzheimer's disease (AD) on the other hand, is commonly believed to affects functional integrity of medial-temporal regions of the brain, leading to progressively decline in episodic memory functions (Buckner, 2004). According to this view, early deficits in episodic memory are symptoms of prodromal AD (Dubois & Albert, 2004).

However, AD is a neurodegenerative disease that leads to atrophy in several brain areas (Buckner, 2004), and very mild or very early AD has also been shown to be associated with decline in attentional orienting (Parasuraman, Greenwood, Haxby, & Grady, 1992) and executive working memory (Braver, Satpute, Rush, Racine, & Barch, 2005). Consistent with these findings, one may assume that early AD can be detected by measures of cognitive control as well. The *APOE*ε4 allele is believed to increase the risk for people with MCI to develop AD (Wang, Hong, Lin, Liu, & Chen, 2010), and may modulate impairments in memory and attentional function for people with MCI (Thorvaldsson et al., 2010). On assays of visuospatial attentional reorienting, patients with mild dementia score worse than older controls (Parasuraman & Haxby, 1993), and *APOE* affect these measures in non-demented people, as healthy *APOE*ε4-carriers score worse than healthy non-carriers (Greenwood, Sunderland, Friz, & Parasuraman, 2000). Thus, measures of cognitive control dysfunctions could be equally good, or better, predictors of incipient dementia or prodromal phases of AD (Negash et al., 2009; Parasuraman, Greenwood, & Sunderland, 2002).

Based on available evidence, the believe of the current study is that normal aging and prodromal AD can be distinguished based on attentional and/or executive working memory task performance. The study will therefore investigate a wide specter of cognitive control tasks, and how they are influence by age, mild cognitive impairment (MCI) and the presence of ε4 polymorphism of *APOE*. A combination of MCI and *APOE*ε4 may in this context be

interpreted as high risk for AD-development, and it is expected that this combination will be associated with severe impairments on attentional and/or executive working memory control tasks.

1.1.1 Research questions and predictions

679 healthy participants, aged 18-79, and 66 patients diagnosed with MCI, aged 46-77 were recruited as part of a bigger project. All participants were genotyped for *APOE* and tested with an extensive battery of neuropsychological tests that are believed to measure diverse aspects of cognitive control (Stroop, Matrix Reasoning, Digit Symbol, Letter-Number Span, TMT A, TMT B). Further, three different behavioral assays generally believed to measure attentional/executive working memory control tasks were selected for this study (experiment 1 is believed to measure covert visuospatial attentional orienting task involving endogenous cues (Posner, 1980), experiment 2 is believed to measure context processing in a continuous working memory updating during stimulus discrimination task (Braver & Barch, 2002), and experiment 3 is believed to measure visuospatial working memory maintenance and resolution in a delayed-match-to-sample task (Greenwood, Lambert, Sunderland, & Parasuraman, 2005)). A behavioral assays is defined as a measure based on cognitive theory, and believed to be more sensitive than standardized neuropsychological tests to measure specific cognitive component processes that are linked to specific functional networks in the brain (Greenwood, Lambert, et al., 2005). Together, these tests and assays made it possible to control and distinguish a wide specter of cognitive control functions and how these were affected by age, MCI and/or *APOE*. Based on previous findings (Ashendorf et al., 2008; Cohn, Dustman, & Bradford, 1984; Greenwood & Parasuraman, 2003; Greenwood, Parasuraman, & Haxby, 1993; Hart, Kwentus, Wade, & Hamer, 1987; Salthouse, Mitchell, Skovronek, & Babcock, 1989), additive main effects of age and MCI were expected on most performances. However, based theoretical considerations (Greenwood & Parasuraman, 2003; Parasuraman, et al., 2002), we expected to find interactions between MCI and *APOE* as well. Since previous studies primarily have found specific effects of early AD and *APOE*ε4 on these subcomponent measures (Braver, et al., 2005; Greenwood, Lambert, et al., 2005; Parasuraman, et al., 1992), we predict to find non-additive effects of MCI and *APOE* only when the *attentional reorienting system* (Corbetta, et al., 2008) is activated, but not on other aspects of control functions. The hypothesis give rise to the following research questions:

1) Can we expect to find non-additive effects of MCI on behavioral assays that specific activate the *attentional reorienting system*?

2) Can an *APOE*ε4 modulation account for such a qualitatively difference?

This introduction will first describe the difference between additive and non-additive effects. Then a general introduction of the currently used behavioral assays are given, including which processes they traditionally are believed to measure, and which neurophysiologic networks that are believed to be involved. For each experiment comments are given on whether previous studies have found additive or non-additive effects of AD-related aging and/or *APOE*, as these findings gave rise to our predictions. After presenting these traditional interpretations, it will be argued how two specific subcomponents in experiment 1 & 3 also can be interpreted in terms of the attentional reorienting system.

1.1.2 Definition: Additive vs. non-additive effects

When comparing healthy aging groups with a pathology patient group on cognitive response pattern, it is often commented about whether the group difference is of a quantitative or qualitative manner (e.g. Braver, et al., 2005; Parasuraman, et al., 1992). In the current study, response patterns in the MCI group are compare with healthy young (YC) and old (OC) participants. MCI and OC groups are age-matched, and the only obvious difference between them is the presence of the MCI diagnosis. Effects of normal aging is therefore defined as (OC ÷ YC), and effects of pathology is defined as (MCI ÷ OC). If MCI is understood as an acceleration of normal aging, then a quantitative difference between MCI and OC are expected on all performances. A quantitative differences is for instance that reaction time decline when measuring (MCI ÷ OC) is similar/proportional to the decline when measuring (OC ÷ YC), or that the oldest individuals in the OC group show a response pattern similar to the MCI group. However, if MCI patterns stand out as something else than a acceleration of normal aging processes, a qualitative differences may be detected. A qualitative differences can for instance be that the difference between MCI and OC can be observed on other measures than difference between OC and YC (see Greenwood, et al., 1993). A quantitative difference between MCI and OC is in this study labeled an additive effect because the MCI diagnosis seem to "add" to the effect of normal aging. A qualitative difference between MCI and OC is labeled non-additive, because response patterns in the MCI group can not be understood in light of normal aging decline. According to the *unitary factor* framework of

aging (Buckner, 2004), one would mainly expect quantitative differences between people with MCI and age-matched healthy control participants. This framework indicate that the same factors that contribute to normal aging, also contribute to AD, and AD represents an acceleration of the same processes that lead to decline in normal aging (Buckner, 2004). As will be discussed later, this framework may be useful to understand the quantitative steady decline pattern between YC, OC and MCI on psychometric test scores and measures of visuospatial working memory. The *multiple factor* framework of aging on the other hand may be useful to understand non-additive effects, as it implies that the factors contributing to AD are different from factors contributing to normal aging, mainly because different brain systems are affected by AD and normal age process (Buckner, 2004). According to this framework, factors leading to normal aging are characterized by reduced function of frontal brain networks whereas factor leading to AD affects the functional integrity of temporo-parietal regions of the brain. Each factor is associated with distinct causes, risk factors, anatomic targets, and cognitive consequences (Buckner, 2004), thus one would expect to find a non-additive effect of MCI on some measures of cognition.

The next section will describe the behavioral assays that have been used to distinguish additive from non-additive effects, and which processes they are believed to measure. Traditionally, these three behavioral assays are believed to measure different information processes unit, i.e. attention and executive working memory respectively. After describing these traditional views, newer theories on how attentional and working memory processes may interact will be introduced, before it will be argued that two different component measures of respectively attentional and executive working memory function in fact may involve the same underlying networks, i.e. the ventral and dorsal frontoparietal networks associated with the attention reorienting system.

1.1.3 Predictions based on three behavioral assays

Experiment 1: Visuospatial Attentional Orienting. The first experiment in this study is believed to measure visuospatial attentional orienting. Posner and Petersen (1990) described the attentional system as an unified system for the control of mental processing. They believe the attentional system to performs operations separately from other mental performances (Posner & Petersen, 1990), and according to this view, a conceptual distinction is made between attentional and working memory functions. The attentional system according

to Posner and Petersen (1990) can be subdivided into three major functional units: *orienting, detecting, and alertness/maintenance* all carried out by different networks of anatomical areas. The first paradigm in this study was first developed by Posner (1980), and is often referred to as a cued letter discrimination task, where an arrow cue is used to direct a persons attention endogenously from one location to another (hence visuospatial attentional orienting). Visual orienting towards a sensory event can be done overtly, for example by direction eye or head toward the object, or it can be done covertly, that is by changing visuospatial attention without eye or head movement (Posner, 1980). The ability to shift attention covertly seems to be modulated by three different areas in the brain, the posterior parietal lobe, the superior colliculus, and the lateral pulivinar nucleus of the posterolateral thalamus, all appearing to have different functions (Posner & Petersen, 1990). Two of these functions are important for the current study: i.e. *engagement vs. disengagement of attention*.

In the experiment participants are presented with arrow cues before asked to respond to a letters identity. A valid arrow cue will direct a persons attention to the right side of the visual field. Most cues are valid, but sometimes an invalid arrow appears that will directed participants attention to the wrong side and will therefore require a participant to redirect attention from one side of the visual field to another (Posner, 1980). The rational is that when measuring the reaction time following a valid cue, the persons ability to *engage attention* to a specific location is calculated, and when calculating the cost of an invalid cue, the persons ability to *disengage/reorient attention* from one location on the screen to another is measured (Posner, 1980). The superior colliculus and the pulivinar is believed to be involved in engagement of attention (Posner & Petersen, 1990), while the parietal lobe is believed to be involved in tasks of attentional reorienting (Posner, Walker, Friedrich, & Rafal, 1984). Thus, the first experiment in this study is believed to map functions associated with the posterior parietal lobe. There is evidence to suggest that the ability to engage attention in response to a valid cue is unaffected by aging (Greenwood, Parasuraman, & Alexander, 1997) or mild dementia (Parasuraman, et al., 1992). Measures of attentional reorienting on the other hand have shown to be sensitive for ageing (Greenwood, et al., 1993), mild dementia (Parasuraman, et al., 1992) and *APOE*ε4 in healthy participants (Greenwood, Lambert, et al., 2005). Indications were given that people with dementia are qualitatively different from age-matched control (Greenwood, et al., 1993; Parasuraman, et al., 1992), and further that healthy *APOE*ε4-carriers are qualitatively more similar to dementia people than healthy non-carriers

(Greenwood, et al., 2000). Thus, one may expect a non-additive effect of MCI+ε4 group on measures of attentional reorienting after an invalid cue to be revealed in the first experiment.

Experiment 2 & 3: Working memory. The second and third experiment in this study are believed to measure of different aspects of working memory. Working memory may be defined as the ability to maintain and manipulate immediate available information (Buckner, 2004). Several subcomponents of the working memory function have been proposed, like the ability to keep information in an active state (up to 30 seconds), to allow manipulation like planning, reasoning, problem solving etc. on a "mental blackboard", and to keep distracters out of this process for the period of active state (Barch et al., 2009; Reinvang, Winjevoll, Rootwelt, & Espeseth, 2010). Baddeley proposed a theoretical model for the working memory, dividing it in three subcomponents, 1) the visuospatial sketch pad, believed to be a short time buffer for visuospatial information, 2) the phonological loop, which is believed to store speech based information, and 3) the central executive function, which is a broader attentional controlling mechanism that guides manipulation of information (Baddeley, 1992; Barch, et al., 2009). It is generally believed that the frontal lobe is involved in executive functions like planning or decision making, and this brain areas are the last to develop during childhood, and the first to be impaired in aging (Craik & Bialystok, 2006). In this study, the executive function of working memory is of most relevance, so the next section will describe experiment 2 and 3 in terms of which processes they are believed to measure, which neurophysiologic networks are believed to be involved, and which effects of age/MCI/*APOE* one may expect to find on these measures.

The second experiment is generally referred to as the AX-CPT task (Braver, et al., 2005). It is believed to measure a function referred to as *context processing/updating* (Braver & Barch, 2002; Braver, et al., 2005). Context processing/updating is the ability to represent the goal of a task while processing and responding to a stream of information, and thus a part of the attentional control function of working memory (Braver, et al., 2005). *Context representation* is defined as any task relevant information that a person has to represent internally in order to perform a task (Braver & Barch, 2002). In short, the person has to respond to the letter X, but only after an A. Thus, an AX trial is the relevant target. A BX trial is one where B represents a invalid distracter (non-A), and requires the participant not to make a target response. The active maintenance of context information is believed to be mediated by the dorsolateral prefronal cortex (DL-PFC), while the dopamine (DA)

projections into the DL-PRF are believed to regulate access to context information (Braver & Barch, 2002). More specifically, DA are believed to filter what information is behaviorally relevant for the task, and which information is to be considered as noise (Braver & Barch, 2002). Thus it is expected that people with damage in either DL-PFC or DA, or both, show impairments on measures of context processing. Neuropsychological studies have shown that responses in the AX-CPT are sensitive to normal aging (Braver & Barch, 2002), AD-related neuropathology (Braver, et al., 2005), and also to *APOE*ε4 effects in healthy adults (Reinvang, Winjevoll, et al., 2010). When comparing healthy younger with older adults, older adults usually score worse than younger adults on trials in this task that involve an invalid cue, are infrequent, and behaviorally relevant (BX trials), especially after a long stimulus onset asynchrony (SOA) (Braver et al., 2001). Also AD-patients show this pattern, but previous studies have not found evidence for a non-additive effect of pathology (Braver, et al., 2005). However, this study did not include *APOE* as a factor. In the current study, additive main effects of age and MCI are expected, but possible non-additive interaction effects of MCI × *APOE*ε4 will be explored, as this was predicted for experiment 1.

The third experiment in this study measures *visuospatial working memory*. This is calculated along two dimensions of demand; load demand and distance demand. Load reflected the number of items participants had to remember, and distance reflected the ability to make correct spatial location distinctions (for details see the methodological section). This experiment does not involve distracters, but tested the ability to store visuospatial information for a short time, and the ability to compare that target location with a new type of spatial location information (i.e. spatial resolution). The latter ability may be seen as a process that involve more executive functions of working memory. Thus, this experiment is likely to involve executive functions in addition to rehearsal function, and one may assume that frontoparietal brain regions are involved in mediating performance on this task. Since normal aging is believed to cause changes in frontal lobe functions (Buckner, 2004), one may expect to find an age-related decline in working memory performance. Greenwood et al. (2005) tested healthy participants and found effects of age and *APOE* on these measures. Thus, effects of age and *APOE* in healthy participants are expected in this last experiment. However, Greenwood et al. (2005) did not include MCI as a factor in their analysis, and therefore possible non-additive interaction effects of MCI × *APOE*ε4 will be explored also in this experiment.

Interaction between attention and working memory. Traditionally, experiment 1 is believed to measure visuospatial attention, while experiment 2 and 3 measure different aspects of executive working memory. This is consistent with general conceptualization indicate that the attentional function and the working memory function are different systems, mediated by different brain regions and modulated by different neurotransmission systems (Greenwood et al., 2008). The cholinergic system modulates the attentional system, and the noradrenergic and dopamergic neurotransmission system are believed to modulate functions of working memory (Greenwood, et al., 2008). However, it is also believed that these two functional systems interact, and newer evidence suggests for instance that certain working memory functions can be improved by cholinergic manipulations (Dani & Bertrand, 2007; Greenwood, et al., 2008). Thus, there is reason to believe that some aspects of the currently used experiments involve corresponding underlying neurological networks.

There are several theories for how visuospatial attention and working memory may interact. Posner and Petersen (1990) believe that attentional alertness may be involved in the short time storage of information. Being in a high state of alertness affect how one can respond to a stimulus (Posner & Petersen, 1990), before storing information for a short time in working memory buffer (Baddeley, 1992). The alertness system can interact with other aspects of the attentional system, as it supports the visual orienting system by giving priority to the processing of different visual information (Posner & Petersen, 1990). Thus, Posner and Petersen propose a functional and anatomical connection between visuospatial attention and alertness attention, a function important for stimulus priority in the working memory. Also Baddeley (1993) argued that working memory involve more than memory processes. He discussed whether *working attention* could be used as term instead of central executive (Baddeley, 1993). Cowan et al. (2005) describe two components of attention as part of working memory: the control of attention and the scope of attention. Control of attention is conceptually similar to Baddeleys central executive and is important for information storage and processing (Cowan et al., 2005). The scope of attention is a conceptualization of the limited capacity of the focus of attention, in form of a typical short time storage of 3-5 chunks of information (Cowan, et al., 2005). Newer theories on working memory agree that visuospatial attention plays a central role in spatial working memory, but disagree on what specific role it plays (Greenwood, et al., 2008). Both studies on nonhuman primates and human subject support the idea that frontoparietal networks modulate short time storage of

location information (Awh, Anllo-Vento, & Hillyard, 2000), and since there seems to be a considerable overlap between frontal and parietal areas in both attentional and working memory task, one hypothesis for the interaction claims that the active maintenance of location information is mediated by attention-based rehearsal (Awh, et al., 2000). Thus, focal shifting of spatial attention may mediate the ability to maintain target locations in the spatial working memory (Awh, et al., 2000). Some evidence that support this attentional-based rehearsal hypothesis come from interference studies. For instance, in a study conducted by Smyth (1996), subjects were asked to maintain spatial information for a short period of time, after which the they were distracted by a spatial and an auditory cue. The spatial, but not the auditory cue interfered with spatial working memory, thus leading to the conclusion that when spatial working memory is interfered by covert shifts of spatial attention, performance declines (Smyth, 1996).

In sum, this means that both conceptual considerations and empirical findings indicate that aspects of the working memory and the attention system interact, both involving frontoparietal networks. In the current study, participants were tested on 3 different behavioral assays that traditionally are believed to measures different systems, thus leading to 3 different predictions of how aging, MCI and *APOE* may influence these measures. However, one may claim that some components of the current assays can be interpreted to measure the same underlying processes, involving the same networks. Both invalid cue trials in experiment 1, and BX trials in experiment 3 can be understood in terms of how they activate ventral and dorsal frontoparietal networks of the attentional reorienting system. The next section will argued how this may be claimed.

1.1.4 New understanding of subcomponents in Experiment 1 & 2: The Attentional Reorienting System

The attentional reorienting system is described as a complex set of adjustments when a novel or unexpected stimuli requires a change in the course of action, and involves interactions between dorsal and ventral frontoparietal networks (Corbetta, et al., 2008). Attentional reorienting may occur between two or more environmental stimuli, and the object to reorient towards has to be salience or behaviorally relevant (Corbetta, et al., 2008). The dorsal network is activated in goal driven tasks (Corbetta, et al., 2008) for instance after many valid cues or an AX trials. The ventral network will interrupt the dorsal network when

expectations are violated and an object sharing features with the relevant target are detected outside current awareness (Espeseth et al., in press). Possible candidates for this activations are stimuli in the oddball paradigm, as evidence from an ERP-study suggest that regions associated with ventral networks are activated by unexpected, task relevant oddball stimuli (Espeseth, et al., in press). Also BX trials in experiment 2, and invalid cue trials in experiment 1 can be interpreted as infrequent and unexpected, but still behaviorally relevant stimuli. Thus one may assume them to activate the attentional reorienting system as well. Experiment 3 and psychometric tests on the other hand are other measures of cognitive control, not specifically involving infrequent, unexpected but behaviorally relevant targets, and thus we do not expect them to be measures of the attentional reorienting system. Do we expect specific non-additive effects of MCI and *APOE* on measures of attentional reorienting? As mentioned above, previous studies have found effects of age and pathology on both paradigms (Braver, et al., 2005; Greenwood, et al., 1993; Parasuraman, et al., 1992), and a qualitative difference was only reported after invalid arrow trials (Parasuraman, et al., 1992). Espeseth et al. (in press) also found *APOE* modulations on ERP-amplitudes associated with attentional reorienting processes, where ε4-carriers had lower P3a amplitudes than non-carriers. Taken together, there is reason to believe that invalid arrow trials in experiment 1 and BX trials in experiment 2 are aspects of one general *attentional reorienting system*, that involves both ventral and dorsal frontoparietal network activation (Corbetta, et al., 2008), as both share features relevant for this activation (unexpected, but behaviorally relevant targets). As previous studies have found specific effects of mild dementia and *APOE*ε4 primarily on measures believed to activate the attentional reorienting system, we predict to find non-additive effects of MCI only when the attentional reorienting system is activated.

After presenting results in this study, the general discussion will then ask if one can argue that the attentional reorienting system is an *endophenotype*, being a intermediate step between *APOE* and AD. But, before turning to the results, important limitations associated with studies involving *APOE* and MCI will be described in the next section.

1.1.5 MCI and *APOE*

When examining the effect of healthy aging compared to pathological aging, it is often difficult to obtain a sample of older adults free from the disease (Buckner, 2004). Healthy older people may be in a stage of pathological development (because of deposits of amyloid

plaques and neurofibrillary tangles) even though no signs of pathology are indicated by cognitive performances (Braak & Braak, 1991). Thus, in the current study one cannot expect to find diametric differences between people with MCI and healthy age-matched controls, because some of the healthy older adults may in fact be in a stage of pathological development. Also, because MCI diagnosis forms a heterogeneous group with unstandardized diagnostic classifications, it may be hard to determine boundaries between normal aging groups and MCI groups (Nordlund et al., 2005). People with MCI usually have normal global cognitive functions and intact daily living abilities, but experience subjectively cognitive deficit usually associated with decline in language, attention or executive function (Grambaite et al., 2011). Amnestic MCI, a subcategory of the MCI diagnosis, is associated with objective impairment in memory performance or both memory and other cognitive performances (Grambaite, et al., 2011). The majority of patients with MCI are called progressive MCI (pMCI) because they will develop AD, but some remain stable in a preclinical phase and are therefore called non-progressive or stable MCI (sMCI) (Vannini, Almkvist, Dierks, Lehmann, & Wahlund, 2007), but these impairments do not meet criteria for dementia (Petersen et al., 2001). Different types of biological markers may increase risk for AD development like cerebrospinal fluid (CSF) markers amyloid β-proteins 42 (Aβ42), or phosphorylated-tau level. The ε4 allele of the *APOE* gene is also concerned to be such a biological marker for increased AD-risk (Mahley, 2006; Wang, et al., 2010; Ye, 2005).

The *APOE* gene is found on chromosome 19 and occurs in three alleles (ε2, ε3, ε4). In a general population, the frequency of ε2 allele is about 5-10%, the ε3 allele about 60-70%, and ε4 between 15-20% (Mahley, 2006; Uterman, Langenbeck, Beisiiegel, & Weber, 1980). The *APOE* gene is believed to be involved in modulations of neuronal repair and plasticity, and hence believed to have a broad effect on cognition (Greenwood & Parasuraman, 2003). The *APOE* gene produces a plasma protein that is involved in the transportation of lipids like cholesterol and other hydrophobic molecules in the central nervous system, and redistributes these lipids among cells throughout the body (Fagan et al., 1999; Greenwood & Parasuraman, 2003; Mahley, 2006). The proteinproduct of *APOE* plays a role in synaptic development (Mauch et al., 2001), and in clearance of cholesterol and other lipids from a site of injury, thus playing a role in long term plasticity changes following an injury (White, Nicoll, & Horsburgh, 2001). When intermediate steps between genotype and cognitive phenotype (i.e. endophenotypes) are considered, it is thought that gene variations can affect cognition through a number of pathways (Greenwood & Parasuraman, 2003). An *APOE* gene has many

functions in the nervous system, and it is generally believed to interact with many demographic, biological and pathological variables, all with multiple consequences for cognition (Reinvang, Winjevoll, et al., 2010). The effect of *APOE* on cognition seem to be different in old and young age (Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Mondadori et al., 2007; Turic, Fisher, Plomin, & Owen, 2001). With respect to AD development, one of the main arguments for how *APOE* is related to degenerative diseases like AD, is that it modulates the way the brain responds to injurious insults like oxidative stress, ischemia, excess amyloid beta production, inflammation, or normal aging process itself (Mahley, 2006). It is believed that the processes of neuronal maintenance and repair are effective in *APOE*ε3 and *APOE*ε2-carriers, but impaired in *APOE*ε4-carriers (Greenwood & Parasuraman, 2003; Mahley, 2006). Previous studies have shown that Aβ42 and *APOE* may interact and influence cognitive control performance in people diagnosed with MCI (Thorvaldsson, et al., 2010). However, *APOE* is just a vulnerability-gene, and being a homozygote ε4 carrier is not sufficient for the development of AD (Henderson et al., 1995). By age 90, only half of the homozygote ε4-carriers have developed AD (Henderson, et al., 1995), and only 60% of people diagnosed with AD (either clinically or postmortem) are believed to be ε4-carriers (Mayeux et al., 1998). This indicated that *APOE* genotyping is not sensitive and specific enough to be used as a diagnostic test for AD (Mayeux, et al., 1998). Furthermore, there is evidence to suggest that being carriers of the ε4 allele increases the risk for developing AD only up to a certain age, and after this peak the risk declines (Breitner et al., 1999).

In sum, when interpreting effects of polymorphic variations of *APOE*, cautions need to be taken because of the general effect *APOE* has in the nervous system, and because the effect of *APOE* on cognition may go through different biological pathways all having different interacting effects on cognition. Thus, as *APOE* may interact with many other variables and influence cognition differently in different time of age, results in this study have to be interpreted with care.

2 Study 1: Psychometric Test Scores

2.1 Predictions

The first part of the study was to examine how age, MCI and *APOE* affected participants scores on different psychometric tests believed to measure aspect of cognitive control. We predicted that main effects of age and MCI would indicate an additive decline of normal aging and MCI on all aspects that measured cognitive control. However, previous studies have reported effects of *APOE*ε4 on executive functions like TMT B or operation span, and on episodic memory, but not on perceptual speed tasks like digit symbol (Small, Rosnick, Fratiglioni, & Bäckman, 2004). We expect therefore to find some effects of *APOE*, but do not expect specific interactions between *APOE* and MCI leading to non-additive decline.

2.2 Method

2.2.1 Healthy control participants

A total of 679 healthy people ranging from 18 to 79 years of age (M = 48.2, SD = 18) were recruited for this study (see table 1 for demographics). Most of the healthy control participants in the control group were recruited through advertisements in local newspapers. Some of the younger participants were students and recruited from different classes at the University of Oslo. The project was approved by the Regional Committee for Research Ethics of South-Eastern Norway. Participants' consent was obtained according to the Declaration of Helsinki (World Medical Assembly, 2008). All participants were screened for previous and present neurological diseases, psychiatric disorders, depression, cancer, chronic illness, substance abuse, sensory or motor impairments all being conditions known to affect the central nervous system. The presence of, or formerly treatment of any of these conditions was used as an exclusion criteria. Healthy candidates were first interviewed by phone according to a checklist about health and previous illness or injuries. Participants had to be native speakers of Norwegian and have completed obligatory basic education without diagnosed reading or learning disorders. Persons on adequate medication for hypertension, diabetes or hypercholesterolemia were not excluded. Participants were not allowed to consume nicotine

or caffeine during the test period or in the lab premises, but were not required to abstain from these substances prior to attendance. All participants read an information sheet and signed a statement of informed consent approved by the regional ethical committee for medical research. All participants completed Beck's Depression Inventory (BDI) (Beck, 1996) as a measure of the presence of symptoms of depression (≥ 13 cut-off criteria for exclusion), as well as screening on the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) to exclude participants by ≥ 26 cut-off criteria.

2.2.2 MCI patients

66 patients diagnosed with MCI (aged 46-77, M = 60.7, SD = 6.8) were recruited by our collaborators at Akershus University Hospital, a memory based university clinic, between September 2005 and January 2010. The inclusion criteria were cognitive symptoms and subjective complaints lasting longer than 6 months, preserved general intellectual function, no or very mild activities of daily living problems (ADL) and Global Deterioration Scale (GDS) score of 2 or 3 (Reisberg, Auer, & Monteiro, 1997; Reisberg, Ferris, de Leon, & Crook, 1988). Diagnosis subjective and mild cognitive impairment (SCI and MCI) (Gauthier et al., 2006; Petersen et al., 1999) were determined from a clinical interview and screening tests, as well as a screening cut-off ≥ 26 on the Mini-Mental State Examination (MMSE) (Folstein, et al., 1975). All participants were given neuropsychological tests (see below) and rated on a standardized protocol. Criteria for exclusion were established psychiatric disorder, cancer, drug abuse, solvent exposure, or anoxic brain damage. The project was approved by the South-Eastern Norway committee for medical research ethics. The MCI sample was stratified according to normal or pathological levels of free flowing amyloid β-proteins 42 (Aβ42), Total-tau (t-tau), and phosphorylated-tau (ph-tau) in cerebrospinal fluid (CFS) extractions, stratification procedures established by age-specific cut-off values (Sjogren et al., 2001). For more detailed information about MCI patients recruitment and screening procedures, see Grambaite et al. (2011).

After screening, all participants (MCI and healthy controls) gave their informed consent to their participation, including blood sampling, DNA extraction, genotyping and the storage of the remaining blood for up to 10 years in a biobank according to Norwegian regulations. The biobank was approved by the Norwegian Department of Health.

Table 1 Demographics

	YC	OC	MCI
N	265	414	66
Male	182 (68.7%)	280 (67.6%)	34 (51.5%)
Female	83 (31.3%)	134 (32.4%)	32 (48.5%)
Education	14,3	14,3	12,5
MMSE	29,3	29,0	missing
BDI	3,7	5,9	missing

NB! MMSE and BDI data for MCI group are missing in this study due to problems with data coordination.

2.2.3 DNA Extraction and Genotyping

DNA extraction and genotyping procedures was conducted initial in the start of this project. Specific details about genotyping procedures, which laboratories were involved, methods used etc. can be found in an article by Espeseth et al. (2006). Following identification of the genotypes of each participant, the total sample was subdivided into two genotype groups: (1) *APOEε4 carriers* (including ε3/4, ε4/4, ε2/4) (2) *APOEε4 non-carriers* (including ε2/2, ε2/3, ε3/3).

2.2.4 Statistical Analysis

All analysis in this study were conducted with SPSS (PASW) Statistics 18, all *p*'s reported are Greenhouse-Geisser values. Participants were tested on Matrix reasoning, Wechsler Memory Scale (WMS) and Vocabulary and subscales of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) on tests of psychomotor speed, attention and executive functions (Trail Making A and B, WAIS-R Digit Symbol, D-KEFS Stroop Color Word (Delis, 2001)), and on California Verbal Learning Test II (CVLT-II) (Delis, 2000). Scores on Vocabulary, WMS & CVLT-II were excluded in this current study, because they are not believed to measure cognitive control functions. Participants were divided into three groups; young control (YC): 18-45 years, N = 265 (M = 28.4, SD = 8, Male/Female = 182/83), old control (OC): 46-79 years, N = 414 (M = 61.3, SD = 8.3, Male/Female = 280/134), and MCI group: 46-77 years, N = 63 (M = 60.7, SD = 6.8, Male/Female = 34/32). Participants were also divided according to genotype, *APOE* (ε4-carrier (N = 269), non-carrier (N = 470). *APOE* was analyzed as a dichotomy variable and not in a three dose manner (non-carriers, heterozygote carriers, homozygote carriers), because a dose analysis would leave too small groups under certain conditions, for instance the MCI ε4/4 carriers would only contain 5 participant. Group (3) and *APOE* (2) were submitting as fixed factors in univariate

ANOVAs, with different psychometric test scores as separate dependent variables. Gender was submitted as covariate for all tests. Not all participants performed all tests. Total number of participants of each tests were: Matrix Reasoning (N = 735), Digit Symbol (N = 680), Letter-Number Span (N = 547), California Verbal Learning Test II (N = 672), Trail Making A (N = 544), TMT B (N = 541) and Stroop test (N= 730). Because of uneven gender distribution in our groups, a non-parametric follow up analysis for chi-square goodness-of-fit was conducted to compare observed gender distribution with expected gender distribution in all three groups. Expected gender distribution, based on official Norwegian non-stratified population count pr. January 2011 (Statistisk sentrabyrå, 2011) was approximately 50/50 (2.460.849 men vs. 2.459.456 women). Chi-square goodness-of-fit analysis were conducted for all participants, and for each group separately. Analysis with CSF-measures were not included, as these were outside of the scope of the predictions in this thesis.

2.2.5 Results

As table 2 shows, the MCI group increased the overall decline observed between YC and OC in an additive way. No *APOE* effects were found in any of the tests.

Table 2 raw scores on all psychometric tests and statistical values

	Young Control	Old Control	MCI	*p*'s	partial eta squared's
Digit Symbol	66,3	50,4	51,4	< .0005	.292
Stroop inhibition	46,1	56,3	66,4	< .0005	.182
Letter Number Span	12,5	10,2	7,9	< .0005	.19
TMT A	24,8	36,9	44,7	< .0005	.233
TMT B	51,4	80,9	95,9	< .0005	.246
Matrix Reasoning	30,5	25,9	17,6	< .0005	.376

Matrix Reasoning. As this test is believed to measure fluid intelligence in relation to adaptive functions, and believed to decline due to age and dementia related brain impairments (Ryan et al., 2005), we expected to find a similar decline due to age and MCI. A rather strong effect of Group was found, $F(2,738) = 219.7$, $p < .0005$, $\eta^2_p = .376$. due to additive decline of age and MCI. This effect did not vary due to gender, when gender was submitted as a covariate ($p = .086$).

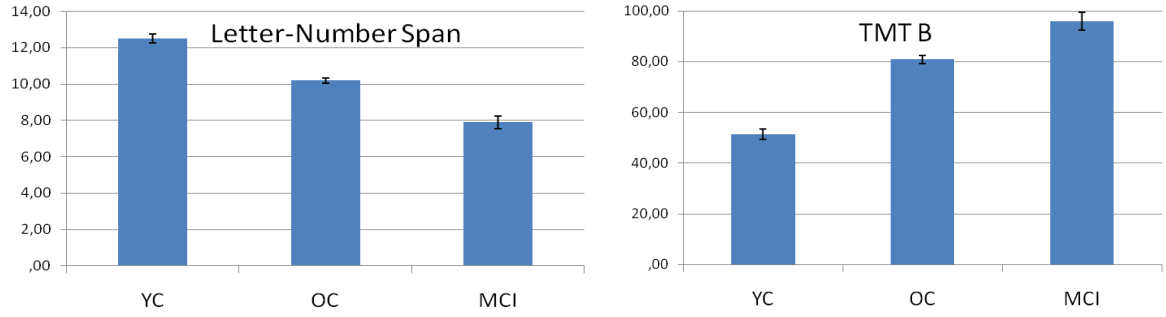
Digit Symbol (WASI-R). This test is primarily meant to measure motor speed performance, but some aspects of memory also make a contribution to performance on this test (Joy, Kaplan, & Fein, 2004). Further, test performance on Digit Symbol is believed to

decline due to age and reflect a general age related slowing of processing capacity (Salthouse, 1996), and MCI patients have been shown to score below age-matched healthy control (Hart, et al., 1987; Nordlund, et al., 2005). We found test performance slowed due to age and MCI, qualified by a main effect of Group, $F(2,673) = 138.9$, $p < .0005$, $\eta^2_p = .292$. However, this effect seemed to be influenced by gender, due to significant covariate interaction ($p = .025$), as performance pattern were in favor of men (M = 56.6 vs. M = 54.5).

Letter-Number Span. Main Effect of Group, $F(2,540) = 63.37$, $p < .0005$, $\eta^2_p = .19$ indicated that this working memory performance also declined due to age and MCI in an additive way, as seen in figure 1.1. Gender did not seem to influence this effect ($p = .112$)

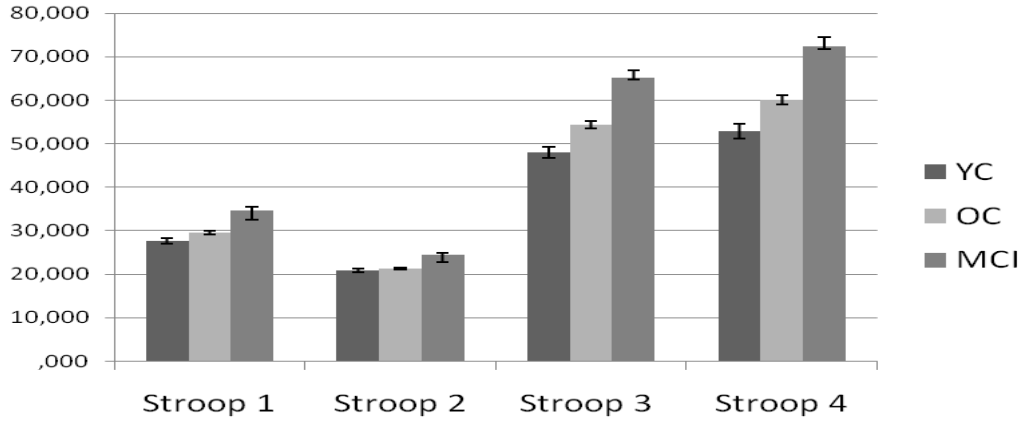
Trail Making Test. Both time on TMT A and B, and error scores on TMT B are useful to distinguish normal aging effects from MCI and AD effects (Ashendorf, et al., 2008). Main effects of Group were revealed on TMT A, $F(2,537) = 81.76$, $p < .0005$, $\eta^2_p = .233$, indicating a steady increase in RT. This effect did not vary due to gender ($p = .821$). Also for TMT B a main effect of Group was found, $F(3,534) = 87.3$, $p < .0005$, $\eta^2_p = .246$, and this effect was similar for both genders ($p = .832$). Figure 1.2 indicate that RT in TMT B increase steady due to age and MCI.

Figure 1.1 & 1.2 Main Effect Group on Letter-Number Span & Trail Making B



Stroop. Especially color naming (Stroop 1) and interference task (Stroop 3) have been shown to be sensitive to effects of aging (Cohn, et al., 1984), and MCI scores are believed to be below age-matched control (Nordlund, et al., 2005). We found main effects of Group with p's <.0005 on all Stroop condition (Stroop 1: $\eta^2_p = .101$, Stroop 2: $\eta^2_p = .083$, Stroop 3: $\eta^2_p = .182$, Stroop 4: $\eta^2_p = .175$). Figure 1.3 show how MCI effect is additive to normal age effect on all measures of Stroop. Stroop condition did not vary due to gender (p's > .233).

Figure 1.3 Main Effect Group on Stroop Tests



Chi-square goodness-of-fit follow up. Chi-square follow up analysis revealed that overall our sample contained more men than expected (67% men, 33% women), χ^2 (1, 801) = 93.045, $p < .0005$. Both the YC and OC group had more men and less women than expected (68.5% vs. 31.5% for YC, and 67.5% vs. 32.5% for OC), while in the MCI group gender distribution was equal (51.5% men, 48.5% women).

2.2.6 Discussion

Indications are given that all psychometric test used showed a pattern of decline due to age and MCI, consistent with a view of MCI being an additive burden to normal aging. No main effects or modulations of *APOE* were found in any of the psychometric tests. Gender did however affect some of the results in significant covariate interactions, and this may influence the generality of these findings. Chi-square goodness-of-fit analysis revealed that compared to what is expected, our sample had an overrepresentation of men and underrepresentation of women in healthy groups, thus indicating that our results may be more representational for men than women in healthy groups. However, the MCI group had an expected distribution of gender.

3 Experiment 1: Visuospatial Attentional Orienting

3.1 Background and Predictions

We predict that performance associated with a MCI diagnosis adds to the decline associated with normal aging on all measures of visuospatial attention that do not activate the attentional reorienting system (i.e. valid, neutral, no cue conditions). Second, we predict that an interaction between MCI and *APOE*ε4 resulting in a non-additive effect on measures that involved attentional reorienting system (i.e. invalid cue condition). The next section it will describe how one can make such specific predictions, based on previous results.

This experiment uses centrally placed cues to indicate in a symbolic way where the target information will be located. Paradigms like this one are believed to elicit top-down processes for spatially attentional orienting (Festa-Martino, Ott, & Heindel, 2004). Attentional impairments in AD patients is commonly believed to be because of damages in the parietal lobe (Parasuraman, et al., 1992; Posner, et al., 1984), or decline in cholinergic integrity (Sarter & Bruno, 2004). It has been speculate if decline in cholinergic density may predict dementia progression, because pathological deposits of amyloid plaques and elevated tau levels have been shown to accelerated decline in cholinergic integrity (Sarter & Bruno, 2004). Taken together, one may expect to find that patient diagnosed with MCI score worse than age matched healthy older adults on overall attentional reorienting measures, and old control score worse than young control. However, previous studies have discussed whether performance of old control and pathology groups are qualitatively or quantitatively different (Parasuraman, et al., 1992). What makes out a qualitative difference? There are many ways to define qualitative vs. quantitative differences between people with mild dementia and healthy controls. Greenwood et al. (1993) addressed this question by examining RTs after valid and invalid cues, and asked if healthy aging groups (age 19 – 79) performance were different compared to response patterns obtained from people with dementia in an earlier study (mean age: 71.8, SD = 2.4) (Parasuraman, et al., 1992). In this earlier study, Parasuraman et al. (1992), found that visuospatial attention in mild demented people was impaired only following an invalid cue and not following a valid cue. Further, this impairment was linked to hypometabolism in the superior parietal lobe in the right hemisphere, indicating that the

impairment of AD was specific rather than global (Parasuraman, et al., 1992). Parasuraman et al. (1992) also included age-matched controls (mean age: 70.7, SD = 2.2) and concluded that there may be a qualitatively difference between healthy aged and demented people in responses following a invalid cue. Greenwood et al. (1993) examined further which factors may contribute to a qualitatively difference in these response patterns, and implemented two tasks on their young and old healthy control groups, 1) a target discrimination task with central cues (endogenous) and 2) a target detection tasks with peripheral cues (exogenous). They found that age difference only became eminent in the discrimination task, as older participants differed from younger participants on RTs for the cost of an invalid cue after a long SOA conditions. On this invalid, long SOA condition, healthy old participants performed better than demented patients, but also that patients with mild dementia had impairments on cue detection task, especially after long SOA (Greenwood, et al., 1993). The authors concluded that this difference in performance indicated a qualitatively difference (Greenwood, et al., 1993). Taken together, these studies imply that SOA and cue validity may be good variables to detect different pattern of performance between normal aging groups and mild dementia groups. In the current study the terms additive vs. non-additive are used difference to describe if effects of MCI are exacerbations of normal aging effects, or if the effect of MCI is something else. As an endogenous discrimination task was implemented, SOA and cue validity were used as variables to distinguish response patterns between young control, old control and MCI groups. We expected that the cost of an invalid cue after long SOA is a plausible candidate for discriminating possible non-additive effects when comparing MCI with OC, and OC with YC. But what about the predicted modulation of *APOE*?

In later years Greenwood et al.(2000) found that healthy *APOE*ε4 carriers showed greater cost of invalid cues compared to healthy non-carriers (Greenwood, et al., 2000). Although the Cost Effect was not as large as for individuals with mild dementia, the *APOE*ε4 carriers showed deficit in visuospatial attention that was qualitatively the same as deficits associated with individuals with mild dementia (Greenwood, et al., 2000). The debate concerns whether these *APOE* modulations in healthy adults is part of a prodromalphase of AD, or whether it can be seen as a cognitive phenotype of *APOE*, independently of AD (Greenwood, Sunderland, Putnam, Levy, & Parasuraman, 2005; Negash, et al., 2009). Another question is how *APOE* may affect the attentional system. One hypothesis claims that *APOE*ε4 affect attention through modulations of the cholinergic system (Parasuraman, et al., 2002). Support for this hypothesis comes from molecular biology, psychopharmacological

approaches, animal studies, behavioral and neuroimaging studies (Everitt & Robbins, 1997). The parietal lobe integrates cholinergic projections, and the efficiency of attentional performances may be dependent on how those projections are integrated in the parietal cortex (Everitt & Robbins, 1997). Prior to clinical diagnosis of AD, decline of metabolic activity and blood flow in the parietal lobe has been found in *APOE*ε4 carriers (de Leon et al., 2001). Thus, there is evidence supporting the hypothesis that *APOE* may influence the reorienting of visuospatial attention in healthy middle aged *APOE*ε4 carriers, and further in people with mild dementia, probably because of decline in cholinergic integrity (Sarter & Bruno, 2004).

In light of the described evidence, we expect to find different response pattern for people with MCI and age-matched healthy participants when measuring the cost of invalid cue. This difference is expected to develop further as SOA increases, and due to the presence of an *APOE*ε4 allele. Further, as the MCI+ε4 group is believed to be at higher risk for AD-development, and because they are general believed to have greater impairments in the medial and parietal lobe (Buckner, 2004), one may expect them to show response patterns that may be different compared to normal aging effects. Because previous findings have indicated that non-additive effects primarily are found on invalid target trials, and because invalid trials are believed to activate frontoparietal networks associated with attentional reorienting system (Corbetta, et al., 2008), we predict a non-additive effect for the MCI+ε4 group specifically for invalid arrow trials. Other cue trials (valid, neutral, no cue) are not believed to activate the attentional reorienting system, and thus we do not predict non-additive effects of MCI in combination with APOEε4 on these trials.

3.2 Method

3.2.1 Stimuli and Procedure

A cued visual discrimination task based on Posner (1980) cued detection task was used. Stimuli were presented on an EIZO 21-in. CRT monitor, and the experimental paradigm was controlled and responses collected by the E-Prime software (Schneider, Eschman, & Zuccolotto, 2002). After a fixation cross (0.45° × 0.45°) was presented centrally on the computer screen for 500ms, a centered arrow cue (1.35° × 0.8°) pointing left, right or in both directions was presented. Also a no cue condition was used. Target consisting of vowels (A,E or U) or consonants (T, D or R) (0.8° × 1.0°, font Tahoma Bold) were presented 6.7° left or

right of the fixation point. The arrow cues were presented at two different target stimuli onset asynchronies (500 and 2000ms). This varied with blocks of trials. Each block consisted of 96 trials and contained 48 valid trials (50%) and 16 trials (16.67%) for each of the other cue conditions. All stimuli were presented in black on a white background. Participants were seated in front of the computer monitor after finishing the informed consent, and the neuropsychological test procedures. An instruction appeared on the screen, and was read out loud for the participant before the practice block started, consisting of 36 trials. Participants were asked to make a categorization of the target letters, pressing the leftmost key with the left index finger on an E-Prime compatible response box as fast and as accurate as possible if the letter was a vowel, and the rightmost key with the right index finger if the letter was a consonant. Each trial began with a fixation cross, followed by a variable SOA, the cue, and finally the target letter. If the participants responded correctly to the target letter, they were notified in terms of the word *Riktig!* ("correct") which was being presented 4° above the center of the screen for 1 second. The participants were given an opportunity for a short break between each block. The whole experiment lasted roughly for 35-40 minuets

3.2.2 Participants and Genotyping

For recruitment, screening, exclusion and genotyping see study 1.

3.2.3 Statistical Analysis

Participants were divided into three groups; young control (YC): 18-45 years, N=262, old control (OC): 46-79 years, N=414, and MCI group: 46-77 years, N = 63. An initial omnibus, repeated measures ANOVA on Accuracy Response was conducted, with Cue Validity (Invalid, Valid, Neutral, No Cue) and SOA (500ms, 2000ms) as within-subject factor, and Group (YC, OC, MCI) and *APOE*-genotype (ε4-carriers, ε4-non-carriers) as between-subject factors. The distribution of participants were as following: YC+ε4 (N=85), YC÷ε4 (N=177), OC+ε4 (N=157), OC÷ε4 (N=257), MCI+ε4 (N=27), MCI÷ε4 (N=36). No follow-up analysis on accuracy measures were carried out, because Accuracy Rate was very high. The second omnibus ANOVA measured Reaction Time (RT) for each condition. An omnibus ANOVA with these factors can give important information about how group differences affected measures on Cue Validity, and about possible modulations on Cue conditions. The effect of aging (OC ÷ YC), can be contrasted to the effect of diagnosis (MCI

÷ OC) on all Cue Condition interactions. Separate univariate follow up for each Cue condition (Invalid, Valid, Neutral, No Cue) was conducted with Group and *APOE* as fixed between-subject factors, and SOA as within-subject factor, aimed to get detailed information about effects on separate cue conditions, and more importantly, to test if invalid cues specifically impaired when MCI and *APOE*ε4 interacted.

The next follow-up analysis aimed to get more information about the contrast effect of attentional orienting. The Total Cue Validity Effect (Invalid Cue ÷ Valid Cue) was calculated to give information about the overall orienting function in visual attention, i.e. how effective a person engages, disengages and moves from one location to another (Posner & Petersen, 1990). The Total Cue Validity Effect holds information about both the RT cost of an invalid cue, and the RT benefit of a valid cue. However, since both people with mild dementia, and *APOE*ε4 carriers are believed to have problems reorienting attention following an invalid cue, but not in engaging attention after a valid cue (Greenwood, Lambert, et al., 2005; Parasuraman, et al., 1992), it is common to calculated further contrast effects for the Cost (Invalid Cue ÷ Neutral Cue) and the Benefit (Neutral Cue ÷ Valid Cue) separately. Also, the Alertness Effect (No Cue ÷ Neutral Cue) was calculated separately as this effect may distinguish if age, genotype or MCI related changes in Cost or Benefit effect are due to actual changes in Cost or Benefit or a byproduct of changes in Alertness (Festa-Martino, et al., 2004).

A third follow-up analysis for normal age groups was conducted. This analysis excluded the MCI group and splitted age group into three levels (Young Age (YA): 18 – 34.4, N = 220, Middle Age (MA): 39.8 – 60.5 years, N = 236, Old Age (OA): 60.51 – 79 years, N = 221). The exclusion of the MCI group, and submitting normal age group factor in an omnibus ANOVA with the same within-subject factors and *APOE*, was rationalized to give more specific information about normal aging effects on visuospatial attention, and how normal aging is modulated by *APOE*-genotype, so we could compare these interactions with the predicted non-additive effect of MCI+ε4 on invalid trials.

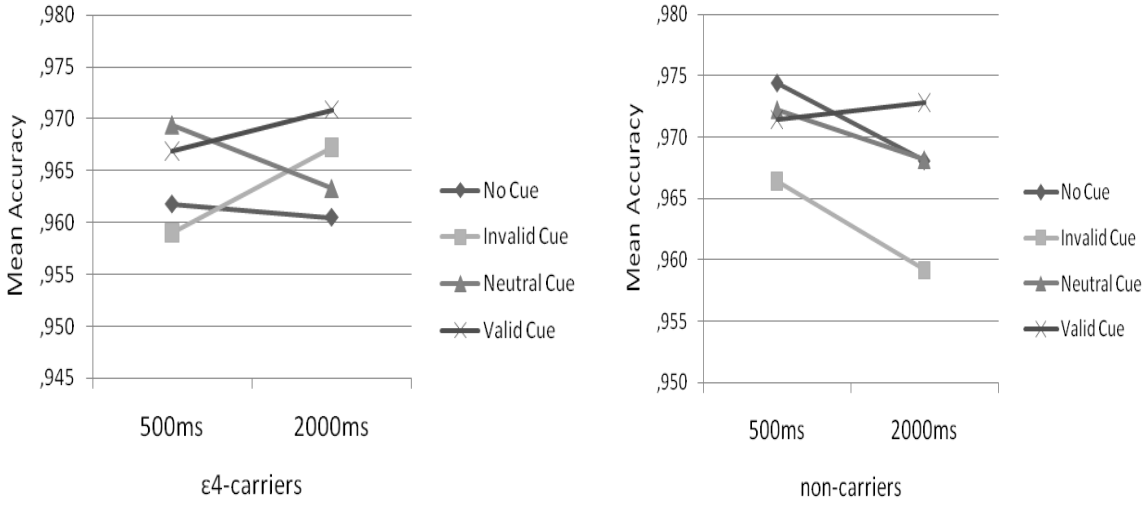
Because we had more men than women in our groups (male = 492, female = 244), we did follow up analysis for Accuracy and RT omnibus ANOVA with gender as a covariate (ANCOVA), to check if the observed effects developed differently when controlling for gender distribution.

3.3 Results

Accuracy. Mean accuracy rates were generally high, ranging from 97.02% to 98.05%. A main effect of Group was found, $F(2,730) = 44.98$, $p < .0005$, $\eta^2_p = .110$, being lowest in the MCI group (.945) and highest in the OC group (.984), and YC having an intermediate value (.973). A main effect of Cue Validity, $F(3,2190) = 7.666$, $p < .0005$, $\eta^2_p = .010$, was also revealed, being highest for the valid condition (.97) and lowest for invalid condition (.963). No main effect of SOA was indicated, but the effect of Cue Validity interacted with SOA, $F(3,2190) = 3.105$, $p = .028$, $\eta^2_p = .004$, longer SOA was associated with higher accuracy for valid cues, but lower accuracy for neutral and no cues.

The effect of Cue Validity was also modulated by *APOE* as indicated by the Cue Validity × *APOE* interaction, $F(3,2190) = 3.51$, $p = .019$, $\eta^2_p = .005$. On average non-carriers showed greater accuracy than ε4-carriers. *APOE* was further involved in an interaction with SOA, $F(1,730) = 4.35$, $p = .037$, $\eta^2_p = .006$, and in the three-way interaction Cue Validity × SOA × *APOE*, $F(3,2190) = 3.25$, $p = .023$, $\eta^2_p = .004$. ε4-carriers differed from non-carriers on invalid cues response after long SOA. As can be seen in figure 2.1a & b, *APOE*ε4 carriers had more correct responses than non-carriers on invalid 2000-SOA condition. However, the differences were very small (from .959 to .967). Group did not modulate any of the within-subject effects.

Figure 2.1a & b SOA × Cue × APOE interaction on Accuracy



Reaction time. A main effect of Group, $F(2,733) = 246.5$, $p < .0005$, $\eta^2_p = .402$, showed that the MCI-group had in general the slowest RT (M = 837.8ms), YC displaying the

fastest (M = 539.6ms), and OC having a value between the two former groups (M = 674.5ms). The omnibus analysis showed no main effect of *APOE,* and no interaction between *APOE* and Group. But, the analyses revealed an expected main effect of Cue Validity, $F(3,2199) = 297.54$, $p < .0005$, $\eta^2_p = .289$. The no-cue condition and invalid were associated with longest RT (M = 700.4ms and M = 697.5ms respectively), the valid cue with the fastest RT (M = 652.7ms), and neutral cue with an intermediate value (M = 685.2ms). Also as expected, the Cue Validity effect developed over time, as indicated by a main effect of SOA, $F(1,733) = 207.381.545$, $p < .0005$, $\eta^2_p = .221$, and a significant Cue Validity × SOA interaction, $F(3,2199) = 6.479$, $p < .0005$, $\eta^2_p = .009$. The reaction time increased in general for all cue-condition when SOA increased, but the effect of SOA was greatest for neutral cues (M = 682.3ms for 500 SOA vs. M = 712.7ms for 2000 SOA), and smallest for valid cues (M = 644.3ms for 500 SOA vs. M = 661ms for 2000 SOA).

A two way interaction showed that the effect of Cue Validity was modulated by Group, $F(6,733) = 16.145$, $p < .0005$, $\eta^2_p = .042$, generally because the difference between valid and invalid cues were smaller in the YC group than OC and MCI group. Group also interacted with SOA, $F(2,733) = 8.181$, $p < .0005$, $\eta^2_p = .022$. SOA effect was largest in the YC group as they increased 21.9ms due to SOA increase (M = 528.6ms for 500 SOA vs. M = 550.6ms for 2000 SOA), OC increased 30.8ms due to SOA increase (M = 659.1ms for 500 SOA vs. M = 689.8ms for 2000 SOA) and MCI increased 17.5ms due to SOA increase (M = 829ms for 500 SOA vs. M = 846.6ms for 2000 SOA).

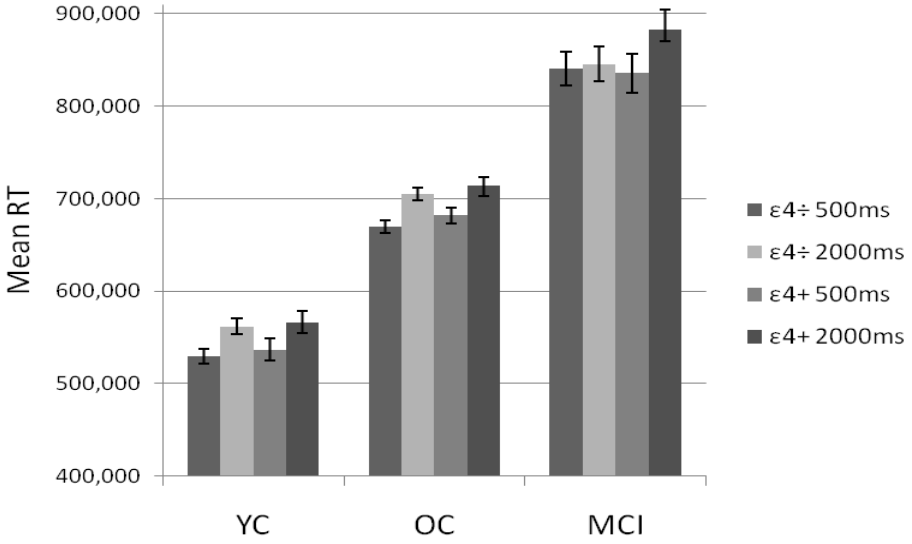
Group was also involved in a three-way interaction with Cue Validity and SOA, $F(6.2199) = 2.988$, $p = .007$, $\eta^2_p = .008$. Generally the increase of SOA increased RT for all groups, with some exceptions. The increase of SOA changed contrast effect of invalid over no cue primarily for the YC group, but not for OC and MCI-group, thus indicating a pattern of response that is specific for people in young age.

APOE-genotype also modulated the effect of the within-subject factors, as indicated in the three-way interaction Cue Validity × SOA × *APOE*, $F(3,2199) = 4.771$, $p = .003$, $\eta^2_p = .006$. Generally, non-carriers were faster than ε4-carriers in all 500 SOA conditions and in some 2000 SOA conditions (invalid, valid), but the mean differences were small (M = 665.1 vs. M = 657.02 for valid, M = 704.16 vs. M = 721.34 for invalid). *APOE* was also involved in the four-way interaction Cue Validity × SOA × Group × *APOE*, $F(6,2199) = 4.255$, $p < .0005$,

η^2_p =.011. The significant four-way interaction in the omnibus ANOVA justified separate analysis for RT on invalid and valid trials.

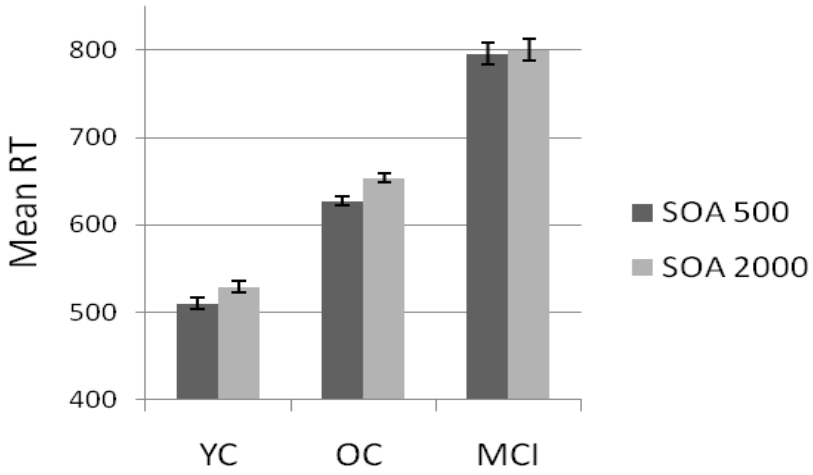
Separate Cue condition follow-up analysis. *Invalid RT*. The RT following an invalid cue increased when SOA increased, $F(1,733) = 120.72$, $p < .0005$, $\eta^2_p = .141$, but this effect of SOA was modulated by *APOE*, $F(1,733) = 4.76$, $p = .029$, $\eta^2_p = .006$. This effect in turn interacted with Group, leading to a three-way interaction, $F(2,733) = 4.79$, $p = .009$, $\eta^2_p = .013$. A closer look at this interaction showed that RT for invalid cues in the 500-SOA condition increased with age and due to MCI, but not due to *APOE* variations. The *APOE* modulation could be observed in the invalid 2000-SOA condition, which showed that the MCI+ε4 group exhibited a longer RT than MCI÷ε4 group (see figure 2.2).

Figure 2.2 SOA × Group × APOE interaction for invalid RTs



Valid RT. For RT following valid cues, main effects of SOA, $F(1,733) = 112.93$, $p < .0005$, $\eta^2_p = .134$, Group, $F(2,733) = 232.55$, $p < .0005$, $\eta^2_p = .388$, and an interaction between SOA and Group was revealed, $F(2,733) = 14.68$, $p < .0005$, $\eta^2_p = .039$. When SOA increased, mean RT increased for YC and OC, but RT increase due to SOA increase was less eminent in the MCI-group. This indicated that when people in the MCI-group engaged and focused their attention following a valid cue, they stayed focused, and RT did not alter due to prolonged SOA (see figure 2.3 for comparing group difference in attentional engagement). No involvement of *APOE* was found for RT following a valid cue.

Figure 2.3 SOA × Group interaction for valid RTs



No cue RT. When no cue were given before target, RT varied according to Group, as eminent in a main effect, $F(2,733) = 234.02$, $p < .0005$, $\eta^2_p = .39$, and leading to a steady increase in RT between the groups. YC the shortest RT (M= 550.5), MCI group had the slowest RT (M= 857.9), and OC the in between value (M= 692.9). A main effect of SOA, $F(1,733) = 69.31$, $p < .0005$, $\eta^2_p = .086$, and an interaction between SOA and Group, (2,733) = 5.89, p = .003, $\eta^2_p = .016$, indicated that a prolonged time of onset without a cue was associated with increase in RT for all groups, but the increase was smallest in the MCI group. Also, the two-way interaction SOA × *APOE* was marginal significance, $F(2,733) = 3.65$, $p = .057$, $\eta^2_p = .005$, and the three way interaction SOA × Group × *APOE* was significant, $F(2,733) = 3.02$, $p = .05$, $\eta^2_p = .008$. In general it appears that ε4-carriers have some longer RT (M=694.8) than non-carriers (M=681.7) when SOA is short, but under a long SOA condition, ε4-carriers and non-carriers RT score is about the same (M=713.5 and M=711.62 respectively). In the three way interaction a short SOA is associated with prolonged RT for all ε4-carriers, but the difference between RT after a short SOA compared with RT after a long SOA was most eminent in the MCI group. Thus when no top down information is given about where the next target is presented, *APOE*-genotype specifically modulates performance in the MCI group.

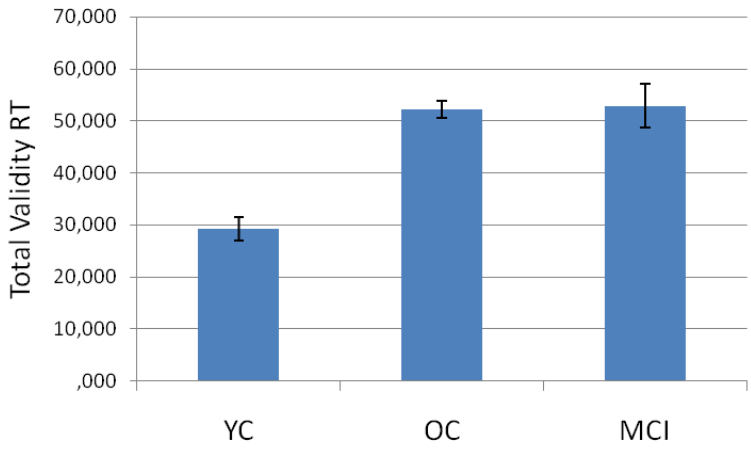
Neutral RT. A main effect of Group after neutral cues, $F(2,733) = 240.29$, $p < .0005$, $\eta^2_p = .396$ showed that the MCI group had the slowest RT (M= 844.1), the YC the shortest (M= 539.7) and the OC the in between value (M= 671.8). Also, a main effect of SOA $F(1,733) = 71.408$, $p < .0005$, $\eta^2_p = .089$, and an interaction between SOA × Group $F(2,733)$

= 5.73, p = .003, η^2_p = .015 were found, indicating that long SOA increased RT for all groups, but slightly more so in the OC group. No main effects or modulations of *APOE* found.

Derived measures of the contrast effects. The modulation of *APOE*, age and MCI were further investigated by separate analysis in form of derived measure of the already mentioned contrast effects. ANOVAs for all four effects were conducted with Group and *APOE* as between subject factors, and SOA as within-subject factor.

Total Validity Effect. A main effect of Group, $F(2,733) = 36.426$, $p < .0005$, $\eta^2_p = .09$ was found for the Total Cue Validity. As can be seen in figure 2.4, the Total Validity Effect increased with age, but not in the MCI-group, showing that a MCI diagnose did not modulate the overall orienting of attention. This pattern was the same for all cue target onset intervals. The effect of SOA became eminent in a main effect, $F(1,733) = 21.59$, $p < .0005$, $\eta^2_p = .029$, indicating that the Total Validity Effect increased with target time onset increase, independently of Group.

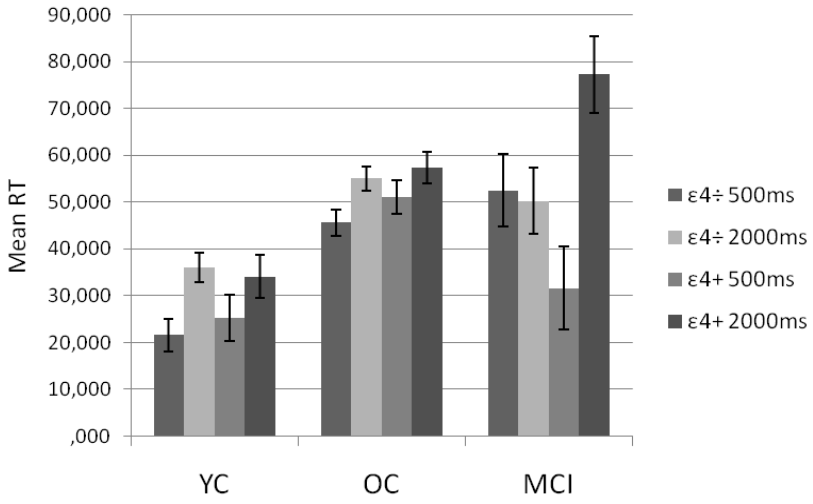
Figure 2.4 Main effect Group on Total Validity Effect



The SOA-effect was however modulated by *APOE*, $F(1,733) = 4.848$, p = .028, η^2_p = .007, revealing that the Total Validity Effect was higher for non-carriers compared to ε4-carriers in the 500-SOA condition, but the opposite pattern emerged in the 2000-SOA condition. In the 2000-SOA condition ε4-carriers had a greater Total Validity Effect than non-carriers . Thus, *APOE* modulated the overall measurement of attentional orienting, but the modulation developed differently on different cue target onset conditions. The *APOE* modulation was further affected by Group, leading to the three-way interaction SOA × Group × *APOE*, $F(2,733)= 5.59$, p =. 004, η^2_p = .015. In this interaction, the modulation of *APOE*

could best be observed in the MCI-group, as MCI÷ε4 had almost the same validity effect for both SOA, while MCI+ε4 clearly showed a significant increase of the Total Validity Effect due to SOA (see figure 2.5). A two-tailed t-test of this difference revealed that it was of marginal significance, $t(61) = -1.874$, $p = .066$.

Figure 2.5 SOA × Group × APOE interaction on Total Validity Effect



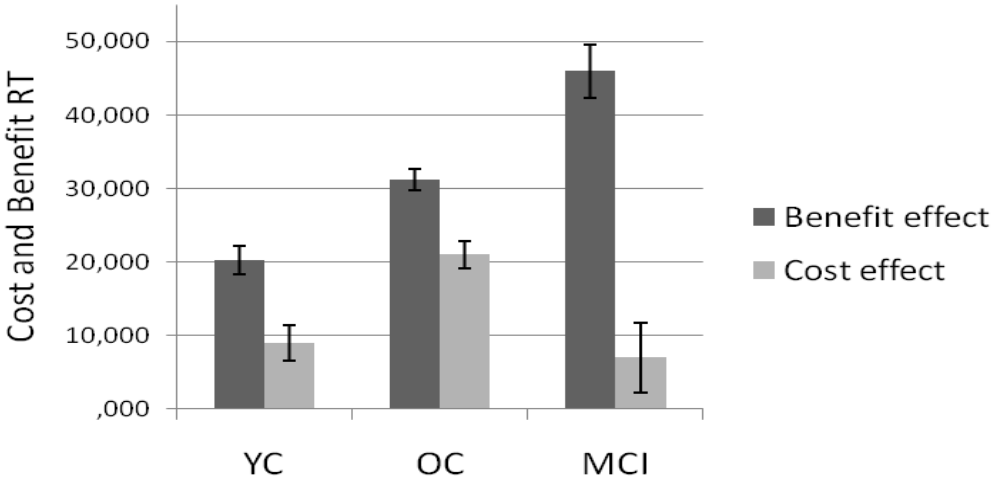
Healthy age analysis. A follow up analysis for healthy age groups was conducted for Total Validity Effect. An increase with age was found, as indicated by a main effect of Age Group, $F(2,671) = 33.03$, $p < .0005$, $\eta^2_p = .090$. YA had the lowest Total Validity Effect (28.6), OA longest (53.6) and MA having an intermediate value (47.5), see figure 2.6. Longer cue target intervals increased the Total Validity Effect in general, as indicated by a main effect of SOA, $F(1,671) = 17.33$, $p < .0005$, $\eta^2_p = .025$, but SOA and Age Group did not interact. *APOE* did not modulate any effects in this analysis, again indicating that the *APOE*-effect is specific for the MCI group.

Figure 2.6 Main effect Age Group

Alertness Effect. A main effect of Group was found for the Alertness Effect, $F(2,733) = 5.56$, $p = .004$, $\eta^2_p = .015$, but this effect distributed itself in a somehow unexpected manner, being highest for OC (M = 21.1), lowest for YC (M = 10.7) and in between the two former for the MCI-group (M = 13.8). The effect of Group developed over time, as indicated by the interaction SOA × Group, $F(2,733) = 4.48$, $p = .012$, $\eta^2_p = .012$. YC had a smaller Alertness Effect after a short SOA, and a longer Alertness Effect after a long SOA, while the MCI-group displayed the reversed pattern. OC had similar Alertness Effect for both SOAs. No effects of *APOE* were found, and a follow-up analysis with healthy age groups found a main effect of SOA, $F(1,671) = 4.43$ $p = .036$, $\eta^2_p = .007$, but failed to find any effects of age or *APOE*.

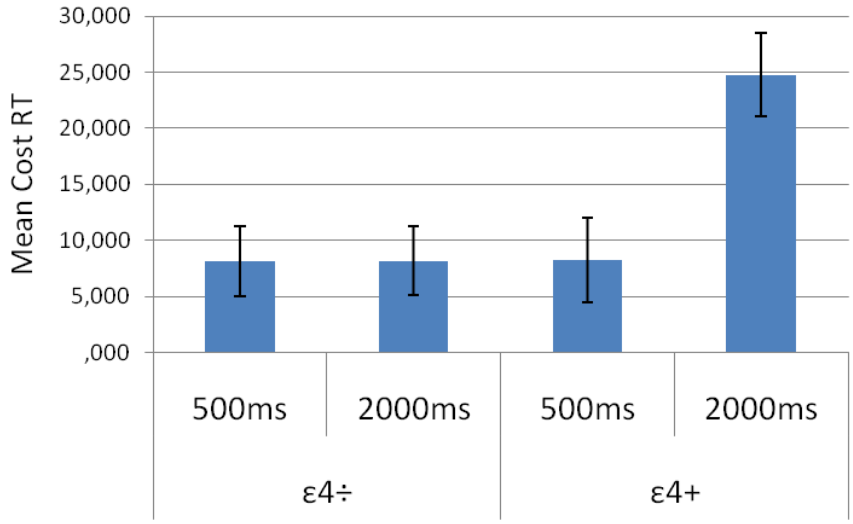
Cost effect. To get a closer understanding of the impairment of attentional shifting due to a invalid target cue, a separate analysis for the Cost Effect of invalid cues, compared with RT for neutral cues was conducted. A main effect of Group was found, $F(2,733) = 9.55$, $p < .0005$, $\eta^2_p = .025$. Cost increases with age, but declined in the MCI-group (see figure 2.7 for Cost and Benefit Effects).

Figure 2.7 Main effect Group on Cost and Benefit



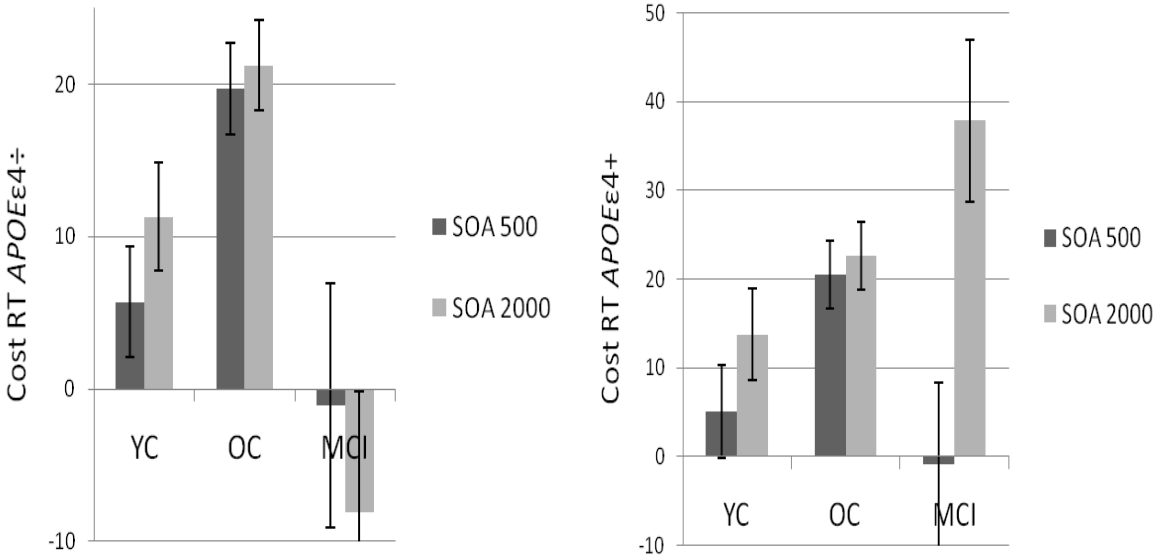
An increase of Cost due to genotype was also observed, indicated by a main effect of *APOE*, $F(1,733) = 4.96$, $p = .026$, $\eta^2_p = .007$. ε4-carriers showed a greater Cost Effect than non-carrier (M = 16.5ms, SD = 2.9 vs. M = 8.14ms, SD = 2.3). Cost also increased with SOA, $F(1,733) = 7.27$, $p = .007$, $\eta^2_p = .01$, and SOA was involved with *APOE* in a two-way interaction, $F(1,733) = 7.19$, $p = .007$, $\eta^2_p = .01$, showing that an increase of SOA clearly affected the Cost Effect in the ε4-carrier group (see figure 2.8).

Figure 2.8 SOA × APOE interaction on Cost



This interaction was further modulated by Group, indicating that the rise of Cost Effect could best be observed in the three-way interaction SOA × Group × *APOE*, $F(2,733) = 3.78$, $p = .023$, $\eta^2_p = .01$. The overall pattern of Cost increase with age and decline in the MCI-group was replicated in the 500-SOA condition. More interestingly, in the 2000-SOA condition the MCI-group splitted according to their genotype. In the 2000-SOA condition MCI÷ε4 demonstrated the same decline as in the 500-SOA condition, but for the MCI+ε4 Cost Effect continued to rise. Mean RT cost was -8.1ms for MCI÷ε4 group, and 37.9ms for MCI+ε4 group in the 2000-SOA condition (see figure 2.9a & 2.9b).

Figure 2.9a & b. SOA × Group × *APOE* interaction on Cost

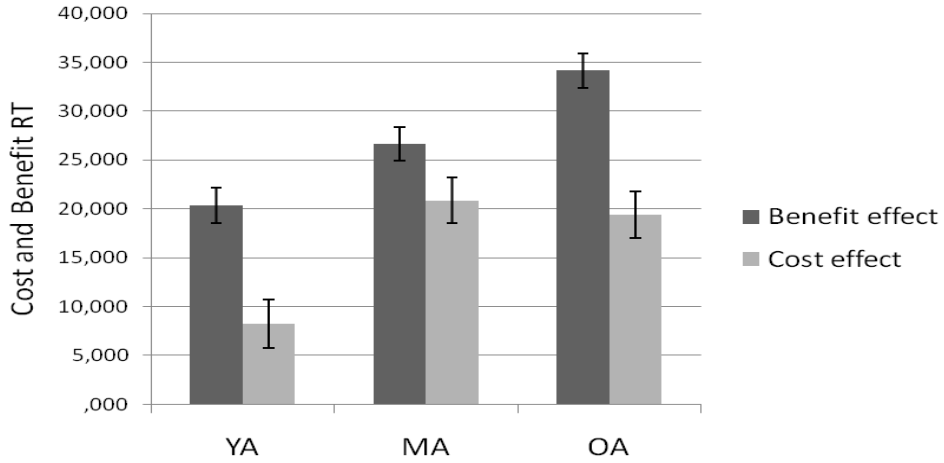


A two-tailed t-tests for this effect revealed that the difference between MCI+ε4 group and MCI÷ε4 group reached a level of significant, $t(61) = -2.313$, $p = .024$. Thus, as with the

separate effect of invalid cues, and the Total Validity Effect, the MCI+ε4 group distinguished itself from the MCI÷ε4 group in the 2000-SOA condition also when Cost Effect was measured. *APOE* was specific involved in modulating the effect of MCI after long SOA.

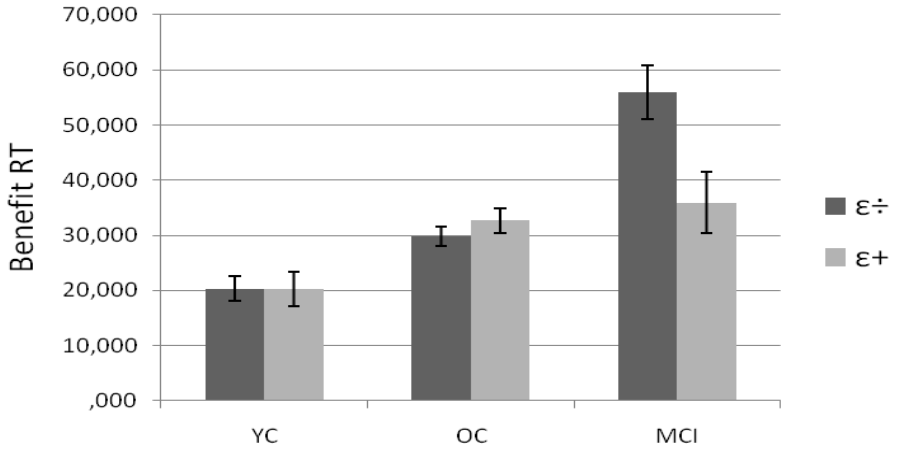
Healthy age analysis. Follow up ANOVA with healthy control group only indicated that the Cost Effect increased with age and stabilized after a certain level, as evident in a main effect of Age Group, $F(2,671) = 8.15$, $p < .0005$, $\eta^2_p = .024$ (see figure 2.10 for Cost and Benefit Effect for healthy age groups). Effects of SOA and *APOE* were not significant in this analysis.

Figure 2.10 Main effect of Age Group on Cost and Benefit



Benefit Effect. A main effect of Group was found for the Benefit Effect, $F(2,733) = 21.97$, $p < .0005$, $\eta^2_p = .057$. As can be seen in figure 2.7, the Benefit Effect increased with age and in the MCI group. A marginal main effect of *APOE* was also revealed, $F(1,733) = 3.81$, $p=.051$, $\eta^2_p = .005$, and a two-way interaction between Group and *APOE*, $F(2,733) = 4.11$, $p = .017$, $\eta^2_p = .011$. As can be seen in figure 2.11, the MCI-ε4-non-carriers had a greater increase in Benefit than the MCI-ε4-carriers. Thus, the MCI+ε4 group had lower Benefit Effect compared to the MCI÷ε4 group, indicating that combination of MCI and genetic risk factor contributed to a decline in the top down advantage of a valid cue to engage attention quickly. However, a two-tailed t-test failed to show that the difference between the MCI+ε4 and MCI÷ε4 was of significance ($p = .115$).

Figure 2.11 Group × *APOE* interaction on Benefit



Healthy age analysis. A further analysis for normal age groups without the MCI group showed the same pattern of steady increase of Benefit Effect due to age (figure 2.10), as indicated by a significant main effect of Age Group, $F(2,671) = 14.82$, $p < .0005$, $\eta^2_p = .042$. The Benefit Effect also increased when SOA increased, $F(1,671) = 6.78$, $p = .009$, $\eta^2_p = .01$, but SOA did not modulate the effect of age, and *APOE* did not modulate any effects in this analysis. Overall, the Benefit Effect was characterized by an overall increase in the normal aging groups, as well as in the MCI-group.

Gender covariate follow up. On omnibus ANCOVA measuring accuracy response, gender covariate was not involved (p's > .243). However, on omnibus ANCOVA measuring RT, gender interacted with SOA, $F(1,732) = 11.399$, $p = .001$, $\eta^2_p = .015$, as RT for men increased more due to SOA increase than RT for women. Gender did alter general effect size on response pattern in some way, as for instance partial eta squared in two-way SOA × Group ANOVA was .022, compared to .035 in the current ANCOVA.

3.4 Discussion

Consistent with previous results, the omnibus ANOVAs showed that endogenous top down information (Cue Validity) about target location affected the accuracy and reaction time responses in covert shifting of visuospatial attention in all groups. Main effects of Group on different measures revealed that normal aging was associated with a decline in accuracy response rate and increase in reaction time, and MCI was associated with further impairment, in a way that might be interpreted as additive. With respect to *APOE* modulations, our results did not replicate previous results showing that healthy ε4-carriers are associated with decline

in visual attention (Greenwood, Lambert, et al., 2005; Greenwood, et al., 2000; Parasuraman, Greenwood, Kumar, & Fossella, 2005). In general we found no modulations by *APOE* in any of the healthy age group analysis, only in interaction with MCI.

With respect to the effects of SOA, previous studies have indicate that a long SOA may reduced inhibition ability in dementia patients (Parasuraman, et al., 1992). Greenwood, Parasuraman and Haxby (1993) have also shown that age effects are best found on longer SOAs. Indications were found that long SOA impaired the ability for visual reorienting for both normal aging and MCI aging processes in generally. The most interesting results were however revealed when Group, *APOE* and SOA interacted on measures of invalid RTs showing that long SOA was associated with largest RT increase in the MCI+ε4 group following an invalid cue.

We predicted to find a non-additive effect of MCI on measures that activate the attentional reorienting system, especially when *APOE* was involved as a modulating factor. Evidence supporting this prediction were found on several levels of analysis involving an invalid cue. On univariate measures of invalid RTs, and on ANOVA measures of Total Validity Effect and Cost Effect it was found that MCI+ε4 showed longer RT than MCI÷ε4, mainly after a long SOA. The effect was interpreted non-additive, because response pattern in the MCI+ε4 group were different than healthy age-matched control and MCI÷ε4 group.

The contrast effects Cost and Total Validity are generally believed to reflect measure of visuospatial reorienting, and captures how efficient someone's ability disengage, and move one's attention from on target location to another (Festa-Martino, et al., 2004). On healthy aging analysis, we found steady increase on the Total Validity Effect. When MCI group was submitted in an ANOVA as one factor, performance was the same as age-matched healthy control participants', thus indicating no effect of MCI on Total Validity measures. A non-additive response pattern on Total Validity measures became only eminent when MCI was stratified according to *APOE* genotype. A combination of MCI diagnosis and being carriers of AD-risk allele, resulted in specific RT impairments on long SOA trials. The MCI+ε4 had greater Total Validity Effect after longer SOAs compared to MCI÷ε4. As no *APOE* modulation were revealed in any normal aging processes, this indicated that *APOE* served as a factor that specifically affected pathological aging processes, giving rise to this differences between normal aging decline and MCI-aging decline. This is consistent with general believes

that *APOE* increases risk for AD-development (Wang, et al., 2010), and affects cognitive performance in MCI and AD-groups more than in healthy control groups (Smith et al., 1998).

With respect to the Cost Effect, we found results that most clearly indicated a non-additive effect of MCI+ε4. The Cost Effect has been shown to be sensitive to dementia and *APOE* modulations (Greenwood, Lambert, et al., 2005; Parasuraman, et al., 1992). Cost Effect is believed to develop steady across normal age (Greenwood, et al., 1993), but patients with mild AD are believed to have greater Cost Effect than healthy controls (Parasuraman, et al., 1992; Parasuraman, et al., 2002; Posner, et al., 1984). More importantly, previous studies have indicated that measures of Cost Effect are sensitive to dementia disease, and that effects of normal aging are qualitatively different from effects of dementia (Greenwood, et al., 1993), an important step for detecting prodromal AD-development. In our study we found evidence for a non-additive effect of AD high risk group (MCI+ε4). A non-additive dysfunction in the attentional system in early AD patients is also consistent with metabolic abnormalities in the parietal lobe which are correlated with AD (Parasuraman, et al., 2002), and neuroimaging studies that indicate that abnormalities in the integrity in the parietal lobe are associated with Cost Effect measures (Parasuraman & Haxby, 1993; Posner, et al., 1984). We found that the Cost Effect increased with age, but only up to a certain level, after which it plateaued. A combination of MCI and *APOE*ε4 contributed to an vast increase of Cost RT (see figure 2.9b). This increase was completely different from the stabilization of response pattern found in healthy age-matched control, and MCI÷ε4 group. Together these finding may indicate that people with high risk for AD-development (MCI+ε4) show a qualitatively different pattern compared to normal age-matched controls in different measures that involved an invalid cue, consistent with our prediction that only measures sensitive to the attentional reorienting system will detect such a difference of possible prodromal AD-development.

On measures after valid cues we predicted to find additive effects of MCI, because only conditions activating the attentional reorienting system were predicted to lead to non-additive effects of MCI and *APOE*. A valid cue is frequent and will therefore not activate the attentional system. Top-down orienting towards goal relevant objects like a valid cue are expected to activate the dorsal frontoparietal network (Corbetta, et al., 2008), but not the ventral. Previous study have found that people with dementia can use such top-down information effectively (Parasuraman, et al., 1992). We found a steady RT increase due to age and MCI on separate univariate measures of valid RTs, consistent with our predictions of an

additive effect of MCI on attentional engagement. We did not find interaction effects of MCI and *APOE* on separate valid cues trials. However, some indications were given that the MCI+ε4 group showed response pattern that was different from MCI÷ε4 and age-matched control when the Benefit Effect was calculated. This observed pattern indicated that MCI÷ε4 responded more similar to OC, and different from the MCI+ε4 group. As these response pattern may indicate a non-additive effect of MCI and *APOE*ε4 on measures of top-down benefit from valid cues as well. This would be in conflict with our prediction, because a valid cue is not believed to activate the attentional reorienting system. A follow up t-test indicated however that the MCI group did not differ significantly due to *APOE* stratification.

On measures of the phasic Alertness Effect, no modulations of *APOE* were found, and the separate neutral cue analysis indicated a stable pattern of increase for all groups. These findings have two important implications: first, it indicates that MCI+ε4 did not show specific effects on alertness measures of attention, and second, it indicated that changes in the neutral cue could not explain the different response pattern observed in Cost. Phasic alerting is elicited by the presence of a cue, in a sense that they give information about that a target will appear soon, and it is believed that the alerting aspect of attention is mediated by ascending noradrenergic projection system originating within the locus coeruleus (Festa-Martino, et al., 2004). Since the Alertness Effect is not specifically modulated by MCI and *APOE*ε4, we may conclude that only an invalid cue trials were sensitive enough to capture early impairments associated with the high AD-risk group.

In sum, we found indication consistent with our predictions. The response patterns in the MCI+ε4 on invalid trials seemed to be non-additive in comparison to normal aging effects. Other measures of attention did not show this effect, indicating that this non-additive effect of MCI and *APOE*ε4 was specific for the attentional reorienting system.

4 Experiment 2: Continuous Working Memory Updating

4.1 Background and Predictions

This experiment include different measures of executive working memory, and a non-additive effects of MCI and *APOE*ε4 is predict only on measures that are believed to activate the attentional reorienting system (i.e. on BX-trials). The following section will introduce the experiment, and based on previous findings, general predictions about effects of normal aging, MCI and *APOE* will be given. At the end of this section it will be turned to how one may argue that BX-trials are similar to invalid arrow cues in experiment 1, and thus probably will elicit the attentional reorienting system.

This experiment is often referred to as the AX-CPT task and is believed to measures context processing/updating capacity (Braver & Barch, 2002; Braver, et al., 2005), i.e. the ability to represent the goal of a task while processing and responding to a stream of information (Braver, et al., 2005). To perform a task, a person has to remember the context representation, or rule. The AX-CPT task requires the participant to make a target response to X, only when it follows an A (Braver, et al., 2005). Thus, for each trial (AX, AY, BX, BY) participants have to keep context information activated to give the correct behavioral response. A context representation like that will bias processing in task performance (Braver & Barch, 2002), as information about what to do when a target appears will make a person predict upcoming cues. The ability to keep this representation of context information activated on-line is important in high load working memory situations where there is a strong competition of response selection, and especially when the appropriate response is infrequent (Braver, et al., 2005). Thus, a person has to know which cues are relevant for the behavior context information expects him/her to perform, i.e. to respond to X after A. This may be seen as quiet a demanding task, and it is shown that measures on this task are sensitive to normal age-related decline (Braver & Barch, 2002), AD-related decline(Braver, et al., 2005), and modulations of *APOE* (Reinvang, Winjevoll, et al., 2010). The current experiment is similar to experiment 1, as it involves manipulations of cue validity. Both valid and invalid cues are presented, and since different effects of MCI and *APOE* were found on invalid vs. valid cues in experiment 1, we expect to find similar patterns also in this experiment.

With respect to valid cues, no specific effects of MCI and *APOE* are expected. The function of letter A in AX trials can be seen as similar to a valid arrow cue in experiment 1. The AX target trial occurs with high frequency in the task (70%) and will leads the participants attention to a particular response bias (i.e. to expect the letter X). The difference is that a valid arrow cue will lead attention in a *visuospatial direction*, while the letter A will lead attention to a *internally set of context rule*. Thus, an AX-trial, like a valid arrow will probably elicit top-down orienting towards goal relevant objects, a function expected to activate the dorsal frontoparietal network (Corbetta, et al., 2008). As previous studies have not reported specific deficit due to age or mild dementia in engagement of attention after a valid cue (Parasuraman, et al., 1992), it is therefore not expected that normal aging and MCI effect measures on AX trials besides general slowing.

With respect to how general aging processes affect different AX-CPT measures, it is commonly believed that the AX-CPT task is able to distinguish different cognitive strategies in aging (Braver, et al., 2001; Braver, Gray, & Burgess, 2007). Braver et al. (2007) distinguished between proactive and reactive strategies. Proactive strategies are implemented in participants with sufficient motivation and/or context updating capacity, as they may tend to "predict" the upcoming stimulus, whereas reactive strategies are believed to be implemented in people with less motivation or capacity (Braver, et al., 2007). When using a reactive strategy, people may wait for the target letter X to appear and then try to remember the identity of the previous letter, so they can determine if the X is a target or not (Braver, et al., 2007). Proactive strategies are believed to be mediated by lateral areas of the PFC and DA midbrain systems, while reactive strategies are believed to be mediated by neural substrates in the anterior cingulate cortex, lateral prefrontal cortex, medial temporal cortex and others (Braver, et al., 2007). In context of this study, it will be predicted that the YC group show a pattern indicating a proactive strategy, while MCI group will show a reactive strategy response pattern.

The response pattern believed to reflect a proactive strategy is: better response patterns on BX trial then on AY trials (Braver, et al., 2005). Increased RT in AY, but decrease in BX trial in young people may reflect an proactive strategy, because when the letter A appears as a cue, young people will expect a X, but as a non-X target appears, they will have to inhibit the expected response pattern. However, when a non-A (B) cue appears, they will exclude target

X, and thus a X after B will not make them activate reactive strategies. Together, one may expect higher RTs after AY compared to RTs after BX in the young control group.

If we assume people with MCI to use more reactive strategies, then one may expect them to have impairments in BX trials as well as AY trials, because a reactive strategy usage in not believed to activate proactive predictions when a B cue appears. Thus, the letter X after B will make people who use the reactive strategy, and thus one may expect specific RT increase in BX-trials. Together, we expect the MCI group to use more reactive strategies than young control group, since they generally are believed to be cognitively more impaired. It will be explored whether *APOE* may modulate the usage of strategy, since the MCI+ε4 in experiment 1 have shown to have more impairments than MCI÷ε4 group.

When calculating proactive/reactive strategy usage, the BX-trial is important because of it's relation to AY-trials. However, this current study is mainly interested in isolated BX-trials response patterns, because it is argued that BX-trials will elicit underpinnings of the attentional reorienting system. Again, like the invalid arrow condition in experiment 1, a BX-trial is believed to activate the attentional reorienting system because expectations are violated, and the target is behaviorally relevant (Espeseth, et al., in press). According to the criteria of unexpectedness, both AY-trials and BX-trials are relatively rare, and involve invalid cues that violates expectations. In fact, previous studies have found that an AY-trial is associated with age-related impairments on both accuracy and reaction time measures (Braver, et al., 2005). However, the Y in AY is not behaviorally relevant, and thus not believed to elicit the attentional reorienting system. Therefore we do not expect specific effects of MCI and *APOE* on AY trials.

The X in the BX trials on the other hand, is unexpected and behaviorally relevant since it is identical to the AX target, hence expected to activate the ventral frontoparietal system to be together with the dorsal system (Corbetta, et al., 2008). RT measures after a BX trials are conceptually similar to invalid arrow cues in the visuospatial attention task, as both measure aspects of the attentional reorienting system, although through different modalities. The question is whether we can expect to find non-additive effects of MCI and *APOE*ε4 on BX trials. As mentioned, Braver et al. (2005) found an steady decline due to age and AD-related pathology on BX-trials consistent with the viewpoint that mild dementia is an additive acceleration of normal aging processes (Braver, et al., 2005). Thus, we expect to find an additive decline of age and MCI when the MCI groups is analyzed as one group. However,

Braver et al. (2005) did not involve genetic factors in their study. It was pointed out that because their study was cross-sectional and not longitudinal, they could not rule out cohort effects (Braver, et al., 2005). Others have also argued that there exists deficits in people with early dementia that are qualitative different compared to cognitive deficits associated with normal aging, and these differences are important for prodromal dementia detection (Morris & Price, 2001; Parasuraman, et al., 2002). Since we found specific *APOE* modulations for the MCI group in visuospatial attentional reorienting, we expect to find specific interactions between *APOE* and MCI on BX-trials. The findings in experiment 1 indicated a non-additive effect of the MCI+ε4 group on cost of invalid arrow cues, thus we expect to find a similar qualitative difference between MCI+ε4 and age-matched control group on BX trials.

4.2 Method

4.2.1 Stimuli and Procedure

Red colored capital letters were presented one at a time in a continuous series on a black computer screen (1° × 1.2° of visual angle, font: Arial). A trial was defined as a pair of letters. Targets were defined as the letter X preceded by the letter A (AX trials). All other letters were considered distracters. AX-target frequency was 70%, thus, the first letter could be taken to be a probability cue for the second. Non-target trials were divided equally between AY, BX, and BY trials (10% each). B and Y in this context mean any other letter than A or X. Stimuli were presented on an EIZO 21-in. CRT monitor, and the experimental paradigm was controlled and responses collected by the E-Prime software (Schneider, et al., 2002). Participants were asked to respond by key presses on an E-Prime compatible response box for every letter presented on the screen. Each letter was presented for 300 ms, and the stimulus onset asynchrony (SOA) was 2000ms. Participants were instructed that correct non-target stimuli response should be given by pressing the left-most key on the response box with the left index finger, and target stimuli (X after A) by pressing the right-most key with the right index finger. Participants were first given a white sheet of paper where a line of red letters was presented, and instructed to practice responses manually by writing either the letter V (initial letter for the Norwegian word *venstre*, meaning left) or H (initial letter for the Norwegian word *høyre*, meaning right) under presented letter. After this manual practice, a practice block on the computer, consisting of 20 trials (40 trials for the patient cohort) was

implemented. The test then contained 6 blocks of 50 trials. All stimuli had to be responded to, but only responses in the time window 100–1500ms after stimulus onset were included in the analysis. The remaining 500ms period before the next stimulus onset was used for auditory feedback where errors were indicated. Participants were instructed that a short beep would occur if they respond inaccurate to keep them concentrated. The experiment lasted 20-30 minutes.

4.2.2 Participants and Genotyping

300 participants in the healthy control group aged 22-77 (M = 54, SD = 14.7), and 57 MCI patients aged 46-77 (M = 60.2, SD = 6.8) conducted this experiment. For recruitment, screening, genotyping and exclusion procedures see study 1.

4.2.3 Statistical Analysis

First we conducted a repeated-measure ANOVA on Accuracy response rate for all conditions. Condition (AX, AY, BX, BY) was submitted as within-subject factor, and Group (YC (22 - 45.4 years, N = 87), OC (45.5 – 76.7 years, N = 212), MCI (46 - 77 years, N = 55)) and *APOE* (ε4-carrier, N = 128, ε4-non-carrier, N = 226) as between-subject factors, leaving six groups: YC+ε4, N=29, YC÷ε4, N=58, OC+ε4, N=78, OC÷ε4, N=134, MCI+ε4, N=21, MCI÷ε4, N=34. The second omnibus ANOVA was conducted with the same variables, but mean of median RTs were calculated for each condition. Also, separate analysis for each condition were submitted in univariate ANOVAs, to get results of possible simple effects of Group and/or *APOE* on specific Conditions.

The next follow up analysis aimed to get a more detailed understanding of normal aging effects on different conditions, and how this may be similar/different from the effect of MCI. For this analysis we excluded the MCI group, and subdivided healthy participants in three groups: Young Age (YA): 22 - 48.7 years, N = 100, Middle Aged (MA): 48.8 – 63.6 years, N = 1000 Old Age (OA): 63.65 – 76.77, N = 99. ANOVAs on overall Accuracy rate, mean of median RTs, and RTs for each condition were submitted in this follow up analysis, with Condition (4) as within-subject factor, and Age Group (3) and *APOE* (ε4-carrier, N = 192, non-carrier, N = 107) as between-subject factor.

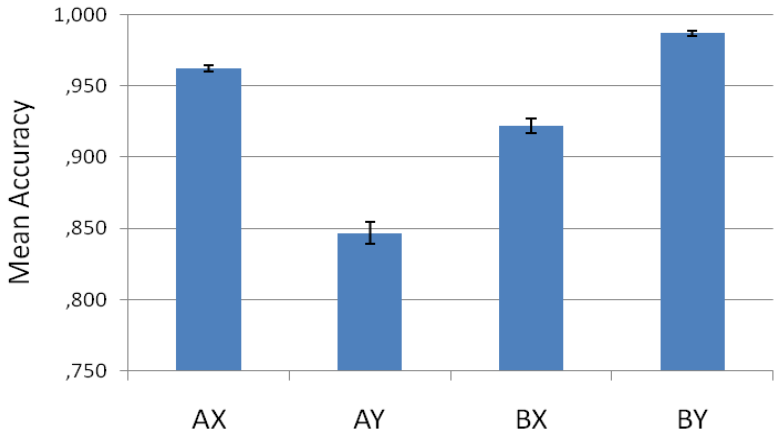
In the third follow up analysis we wanted to get a clearer picture for between-group effects on Conditions of interest for attentional reorienting (BX and AY). We controlled for effects of baseline (AX), by calculating the proportional effect of each groups RT on respectively AY, BX, BY. This was done by calculating three Condition within-subject factors 1:AYprop (AX-AY/AX), 2: BXprop (AX-BX/AX), 3:BYprop (AX-BY/AX). Group (3) and *APOE* (2) were submitted as between-subject factors.

Also in this experiment we did a follow up analysis for all omnibus ANOVAs with gender as a covariate (ANCOVA) (male = 228, female = 126), to check if the observed effects developed differently due to gender.

4.3 Results

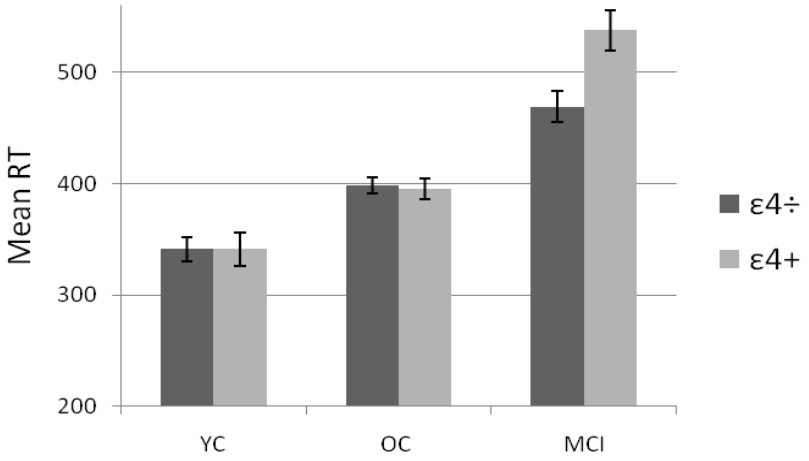
Accuracy. As expected, there was a significant main effect of Condition, $F(3, 1044) = 189.5$, $p < .0005$, $\eta^2_p = 0.35$, due to lower accuracy in AY (85%) and BX (92%) trials, than in AX (96%) and BY (99%) trials (see Figure 3.1). There were no other significant main effects or interaction effects in this ANOVA (p's > 0.1). However, there was a marginal effect of Group on BX accuracy in a univariate effects follow up analysis, $F(2,348) = 2.71$, $p = .068$, $\eta^2_p = .015$, indicating that YC had highest accuracy (M = .936), MCI the lowest (.904), and OC intermediate score (M = .926) on BX-trials. Group also interacted with APOE on BX-trials, F(2.348) = 3.423, p = .034, $\eta^2_p = .019$, indicating that MCI group had the clearest drop in accuracy rates due to genotype (M = .927 for ÷ε4 vs. M = .88 for +ε4). On univariate ANOVA for AY-trials, no significant main or interaction effects were found for. On univariate ANOVA for AX-trials however, a main effects of Group was found, $F(2,348) = 6.88$, $p = .001$, $\eta^2_p = .038$, and similar effect for BY-trials, $F(2,348) = 3.214$, $p = .041$, $\eta^2_p = .018$, both revealing a pattern were OC had the highest accuracy, MCI the lowest, and YC the intermediate value. However, differences were small (e.g. difference between OC and MCI on BY trials were .992 vs. .982).

Figure 3.1 Main effect Condition on Accuracy Rates



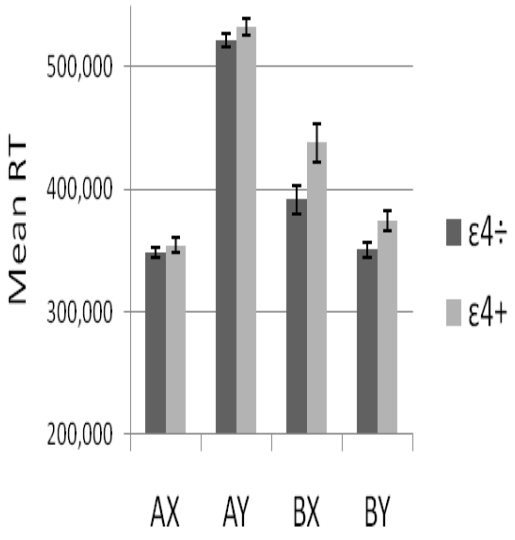
Reaction time. There was a significant main effect of Condition, $F(3, 1044) = 396.6$, $p < .0005$, $\eta^2_p = .53$. RTs were longer in AY (M = 527 ms) and BX (M = 415 ms) trials than in AX (M = 351 ms) and BY (M = 363 ms) trials. There were also significant main effects of *APOE*, $F(1, 348) = 4.3$, $p = .039$, $\eta^2_p = .012$, were ε4-carriers were slower than non-carriers (M = 402.97 vs. M = 424.82). Also, a main effect of Group, $F(2, 348) = 61.0$, $p < .0005$, $\eta^2_p = .26$. showed that YC were faster than OC, and OC faster than the MCI group (M = 341.2, M =397.2, M = 503.3). Group and *APOE* interacted in a two-way interaction, $F(2, 348) = 4.0$, $p = .018$, $\eta^2_p = .023$, due to the fact that *APOE* only had an effect in the MCI group (see figure 3.2). The steady increase in RT for all groups was also found in separate univaritate follow up analysis for AX, AY, BX and BY. For separate BX, a main effect of *APOE*, $F(1, 348) = 5.528$, $p = .019$, $\eta^2_p = .016$, and interactions between Group and *APOE*, $F(2, 348) = 5.688$, $p = .004$, $\eta^2_p = .032$ were found, indicting a similar pattern: ε4-carriers were slower than non-carriers (M = 391.5ms vs. M = 437.9ms), a difference mainly attributed to slowing in the MCI group (M = 476.5ms for ÷ε4 vs. M = 626.5ms for +ε4).

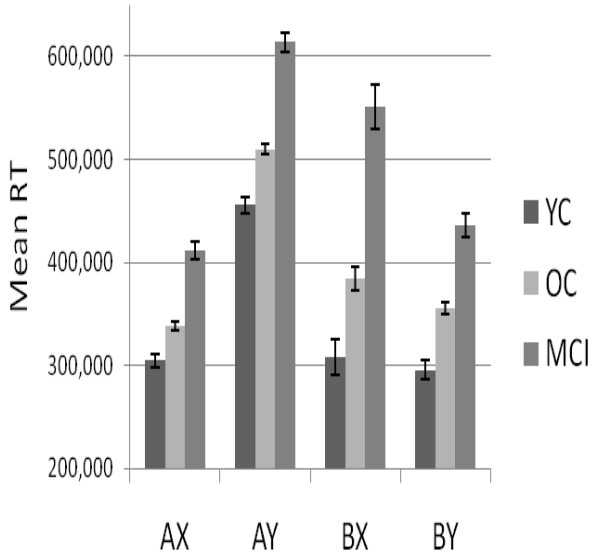
Figure 3.2 Group × APOE interaction



In the omnibus ANOVA, there was also a significant Condition × *APOE* interaction, $F(3, 1044) = 5.0$, $p = .012$, $\eta^2_p = .014$, due to longer RTs on BX and BY-trials for ε4-carriers (figure 3.3). There was also a significant Condition × Group interaction, $F(6, 1044) = 14.6$, $p < .0005$, $\eta^2_p = .077$, showing that the MCI group were slower than OC and YC, particularly on BX trials (see figure 3.4).

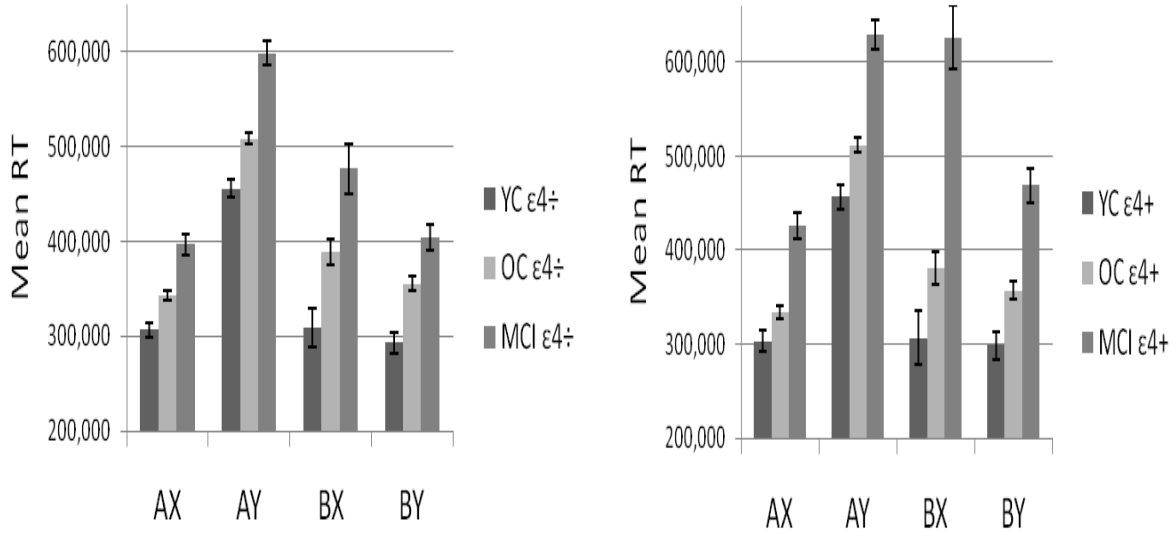
Figure 3.3 Condition × *APOE* interaction & Figure 3.4 Condition × Group interaction





Interestingly, there was a significant three-way interaction (Condition × Group × *APOE* interaction), $F(6, 1044) = 4.9$, $p = .002$, $\eta^2_p = .027$. Figure 3.5a and b show that MCI patients are overall slower than OC and YC, and OC slower than YC in all conditions for both ε4-carriers and non-carriers .The MCI+ε4 group clearly stands out as slow on BX-trials compared to MCI÷ε4 group and OC groups.

Figure 3.5a & b Condition × Group × *APOE* interaction



Healthy age analysis. The follow up omnibus ANOVA with healthy age control was conducted to compare more detailed effects of normal aging with observed MCI effects. For mean accuracy data there was a large main effect of Condition, $F(3, 879) = 239.9$, $p < .005$, $\eta^2_p = .45$. No main effects of Age Group or *APOE* were found. However, there was also a Condition × Age Group interaction, $F(6, 879) = 2.3$, $p = .031$, $\eta^2_p = .016$, as the MA group had higher AY accuracy than OA and YA participants (see figure 3.6). In addition, there was a significant Condition × *APOE* interaction, $F(3, 879) = 4.1$, $p = .026$, $\eta^2_p = .014$. Figure 3.7 shows that ε4-carriers had lower accuracies in AY-trials, but there were no differences in the other three conditions. There were no further significant results in this analysis.

Figure 3.6 Condition × Age Group interaction

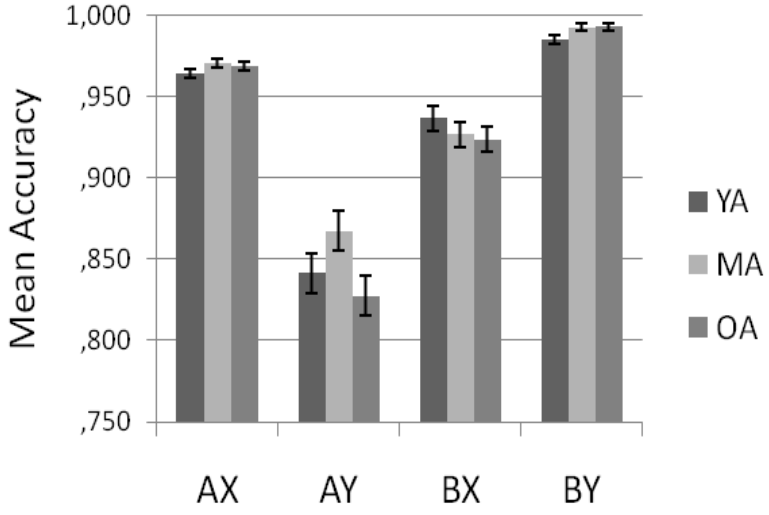
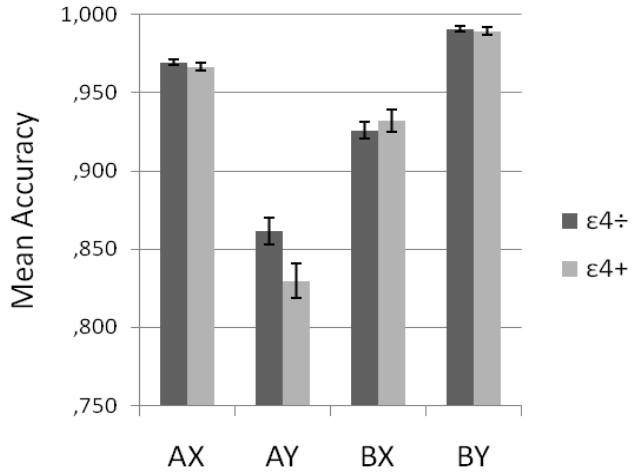
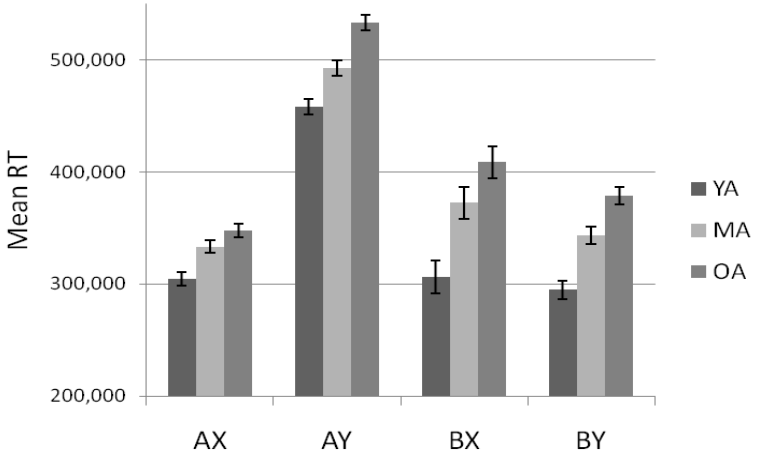


Figure 3.7 Condition × *APOE* interaction



For analysis on RT data in healthy control groups, there was a strong main effects of Condition, $F(3,879) = 505.9$, $p < .0005$, $\eta^2_p = .63$, and of Age Group, $F(2,293) = 24.1$, $p < .0005$, $\eta^2_p = .14$, but no main effect of *APOE* ($p = .86$), or *APOE* × Age Group interaction ($p = .96$) were revealed, confirming that *APOE* has no impact on RT performance among healthy controls. There was a significant Condition × Age Group interaction, $F(6, 293) = 4.87$, $p = .002$, $\eta^2_p = .032$. Figure 3.8 shows that this interaction pattern is different from the same interaction pattern when MCI are included (figure 3.4), as none of the healthy control groups showed a specific RT increase on BX-trials compared to AY-trials. On separate univariate follow up analysis for each trial, main effects of Age Group (p's < .0005), but no effects of *APOE* were found for all trials. A pattern of steady RT increase due to age were found for all trials. On separate BX-trials RTs for groups were: YA = 306ms, SD = 14.4, MA = 372ms, SD = 14.4, OA = 408ms, SD = 14.3.

Figure 3.8 Condition × Age Group interaction



Proportional RTs follow up. When controlling for effects of baseline (AX) on reaction time for AY, BX and BY, effect of between-group factors became even clearer. Main effects of Group, $F(2,348) = 14.453$, $p < .0005$, $\eta^2_p = .077$, and *APOE*, $F(2,348) = 7.024$, $p = .008$, $\eta^2_p = .02$ revealed a similar pattern as above. As can be seen in figure 3.9, showing two-way interaction Group × Condition, $F(4,696) = 10.405$, $p < .0005$, $\eta^2_p = .056$, effect of MCI on BX-trials became more distinct when controlling for baseline. Group and Condition also interacted with *APOE* in a three-way interaction, $F(4,696) = 3.769$, $p = .014$, $\eta^2_p = .021$, indicating the same pattern as above. MCI+ε4 clearly exhibited a different response pattern on BX-trials compared to MCI-non-carriers and OC group (figure 3.10b).

Figure 3.9 Group × Condition interaction – proportional RTs for each group

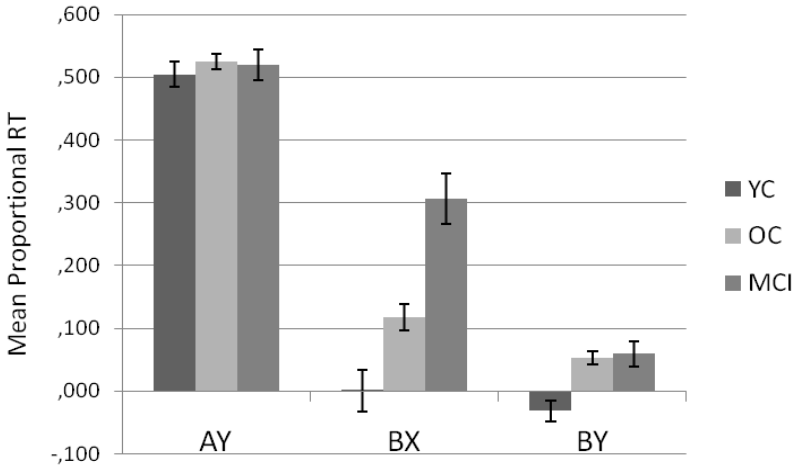
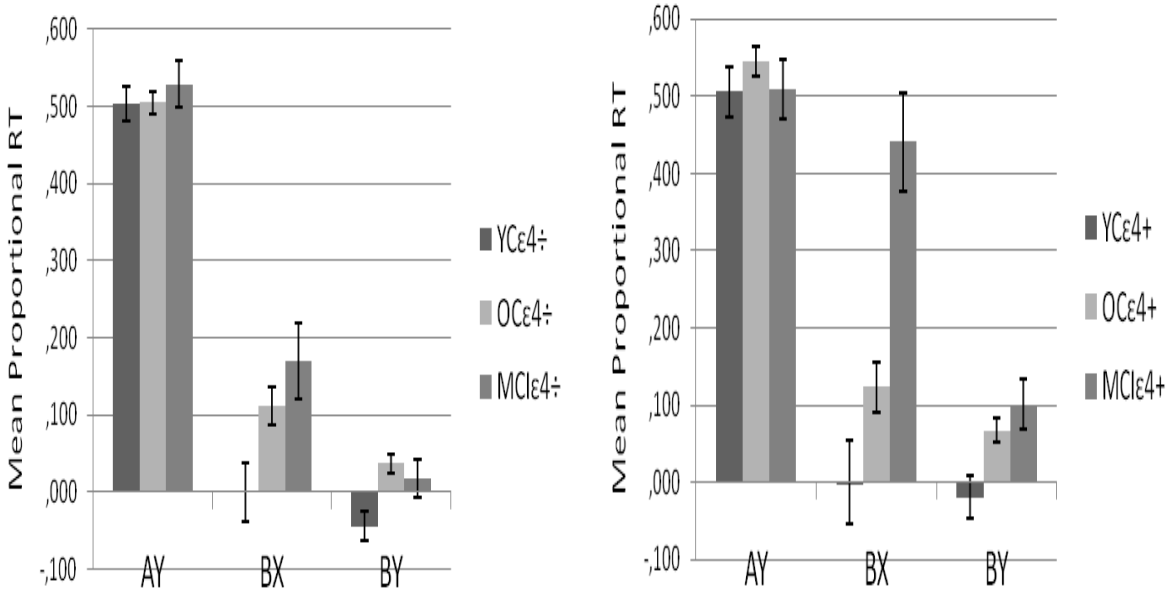


Figure 3.10a & b Condition × Group × APOE interaction - proportional RTs for each group



Gender covariate follow up. On ANCOVA measuring accuracy response rate, gender was involved as a main effect, $F(1,350) = 6.687$, $p = .01$, $\eta^2_p = .019$, and with Condition, $F(3,1050) = 6.029$, $p = .005$, $\eta^2_p = .017$, and on omnibus ACNOVA measuring reaction time, gender was only involved with Condition, $F(3,1050) = 6.664$, $p = .003$, $\eta^2_p = .019$, indicating that men had more correct than women (M = .937, SD = .003 vs. M = .925, SD = .004), mainly due to differences in AY-trials, whereas on RT measures on the other hand, men were faster on all conditions except AY-trials.

4.4 Discussion

The results revealed an expected main effects of Condition for both accuracy and reaction time. There were also clear main effects of Group, YC scoring faster than OC, and OC faster than MCI on RT measures, and on univariate BX accuracy measures a pattern of decline due to age and MCI appeared. Braver et al. (2001) found that older adults were faster and had more correct responses than younger control on AY-trials. We did not find evidence for this in accuracy measures including MCI, but on accuracy measures involving only healthy adults, we found a curvelinear relationship between YA-MA-OA, indicating that middle aged controls had more correct responses than both young control, and old controls. According to valid cues (AX-trials), no specific effects of age and MCI besides general slowing were predicted. Results gave evidence for this predictions, as RTs on AX-trials increased steady across healthy age groups, and due to MCI, regardless of *APOE* possessions.

The AX-CPT task is also believed to be able to distinguish proactive and reactive cognitive strategies in aging (Braver, et al., 2007). The YC group was predicted to show patterns indicating proactive strategies (i.e. higher RTs on AY than on BX-trials). Evidence was found that not only the YC group, but also the OC group used more proactive strategies, as healthy age follow up revealed that all age groups had higher RTs on AY than on BX-trials. It was also predicted that people with MCI used more reactive strategies, as impairments in BX-trials as well as AY-trials were expected for this group. Results from omnibus ANOVA measuring RTs showed that MCI group had higher RTs on AY-trials than on BX-trials, thus contradicting the prediction and indicating that the MCI group as a whole used proactive strategies. However, the difference between AY and BX-trials were smaller compared to what was found for YC and OC groups. When stratifying the MCI group

according to *APOE*-genotype, a different pattern emerged, i.e. the MCI+ε4 group had similar RTs for both AY and BX-trials, indicating that this group uses more reactive strategies.

The final prediction concerned a non-additive effect of MCI and *APOE* on BX-trials only, as the MCI+ε4 group is believed to have highest risk for AD-development (Wang, et al., 2010), and because BX-trials are believed to activate the attentional reorienting system. Consistent with Braver et al. (2005) evidence was found that people most likely to develop AD (i.e. the MCI+ε4 group) had longer RTs on BX compared to MCI÷ε4 and age-matched control (see figure 3.5b). The healthy age follow-up analyses excluding MCI patients indicate that this effect was not associated with normal aging, and the MCI÷ε4 groups response pattern was more additive to normal aging decline. Braver et al. (2005) concluded that their data indicated mild dementia process as an acceleration of normal aging processes (Braver, et al., 2005). However, their study did not involve genetic factors. Finding from the current study indicate that when genetic factors are included in the analysis, one can distinguish a qualitatively different response pattern for the group that is most likely to develop AD on BX-trials.

Conflicting with our predictions, the RT omnibus ANOVA indicated that MCI+ε4 group revealed non-additive pattern qualified by a likely reactive strategy usage in the MCI+ε4 group (i.e. same RTs for BX and AY-trials). However, as mentioned above, the main interest of this study was isolated BX-trials RTs. The Y in AY-trials is not behaviorally relevant, and thus not likely to activate the attentional reorienting system. In follow up analysis controlling for AX-baseline effect, the specific effect of MCI+ε4 on AY-trial RTs disappeared. In this follow up, the MCI+ε4 group also indicated a proactive strategy usage. Taken together this indicates that specific increase in BX-trial RTs seems to be more robust than effects on AY-trials. Also, the effect on BX-trials is limited to individuals with high risk for AD (MCI+ε4). This result is similar to what was found on Cost Effect of MCI+ε4 in experiment 1. The similarities are due to behaviorally relevant target that are was preceded by an invalid cue. *APOE*ε4 modulated the effect of MCI diagnosis in a way that distinguished this group from normal aging pattern, and from MCI÷ε4s performance. This is consistent with our predictions, as we expected to find non-additive effects of MCI and *APOE*ε4 only on these measures, indicating that measures of the attentional reorienting system are sensitive to detect possible prodromal AD-development.

5 Experiment 3: Visuospatial Working Memory

5.1 Background and Predictions

Evidence from both structural imaging studies and genetic studies indicate that changes in the frontal-stratial areas and changes in the medial temporal lobe are factors influencing age-related decline in executive function and memory functions (Buckner, 2004). The aim in with this experiment was to ask if MCI and *APOE* affected measures of visuospatial working memory differently than measures that activate the attentional reorienting system. It was investigated if and how normal aging processes can be differentiated from MCI-related aging processes on measures of visuospatial working memory, as previous studies have shown a decline in working memory function due to age and early AD (McKhann et al., 1984; Salthouse, et al., 1989). Because *APOE* modulations were found specifically for the MCI group in experiment 1 and 2, one may ask if the presence of an *APOE*ε4 allele affects the performance for healthy individuals and/or people with MCI differently on current working memory measures as well. Previous studies have indicated that healthy ε4-carriers exhibited deficits in both visual and non-visual measures of working memory recall (Bondi, et al., 1999; Greenwood, Lambert, et al., 2005; Reinvang, Winjevoll, et al., 2010), so one would expect to find modulations of *APOE* in healthy participants, and even in the MCI group as this was revealed in experiment 1 & 2. However, this experiment does not involve infrequent and behaviorally relevant targets that may activate the attentional reorienting system, and according to our initial prediction, we do not expect to find specific non-additive effects of MCI+ε4 on current measures of visuospatial working memory.

5.2 Method

5.2.1 Stimuli and Procedure

A spatial working memory based on Greenwood et al. (2005) was used. Stimuli were presented on an EIZO 21-in. CRT monitor, and an E-Prime software (Schneider, et al., 2002) controlled the experimental paradigm and collected responses data. After a fixation cross

which was presentation for 1 second on the center of the screen, one, two or three black target dots (.67° in diameter) appeared at random locations on the screen, and stayed for 500msec. After the black dots disappeared, a new fixation cross appeared in the center of the screen and lingered randomly for either 2.5sec, 3sec or 3.5sec. After this delay a single red dot appeared on the screen. This red test dot appeared either at the same location as one of the black target dots (match condition), or at a different location (non-match condition). Non-match condition varied with three levels of distance (about 2°, 4° or 8° apart from the red dot), and participants were asked to decide whether the test dot location matched one of the target dots. Total trials of 252 were distributed over 4 block, each block consisted of 63 trials and contained 23 match trials, 13 non-match close distance trials, 13 non-match medium distance trials, and 13 non-match long distance trials. Participants were seated in front of the computer monitor with the response box between their hands. An instruction appeared on the screen, and was read out loud for the participant before the practice block started, consisting of 21 trials. Participants were asked to remember the target location/s of the black dot/dots, and compare the first location/s to the location of the red dot. If the red dot appeared on the same spot as one of the target locations, they were asked to press the leftmost key with the left index finger as fast and as accurate as possible. But if the red dot appeared not on the same location as one of the black dots, they were to press the rightmost key with the right index finger. Participants were notified extra for the non-match close distance condition, and told that when red and black are not presented in the same location, the difference between them can be quiet small (about 1.5cm). Participants were given the opportunity for short breaks between each block. The whole experiment lasted roughly for 30-35 minuets.

5.2.2 Participants and Genotyping

A total of 364 people participated in this study. Some problems with extreme outliers in the accuracy response rate (below 1% in some distance conditions) called for exclusion action. Different cut-off criteria for exclusion were inspected. First a 50% accuracy cut-off rate for all distance conditions was tried, but this would leave a relatively small MCI group (40 out of 50). Other cut-off procedures were tested, for instance a minimum 30% correct response on all non match condition and 50% on match condition but this still left a small MCI group (N = 44). Another cut-off procedures was to exclude all who had less than 1 correct response on all non-match and load conditions, and 50% correct accuracy rate on

match condition, but this would still leave out 10% of the MCI group (N=45). In the end it was concluded that no good cut-off criteria can be met without loosing important information about the MCI group. Thus, a 50% accuracy response rate cut-off for all load condition on match trials was admitted, thereby excluding 2 participants in the young control group, 4 in the old control group, and 5 in the MCI group. Also, a 50% accuracy response rate cut-off was applied for all load condition on non-match trials collapsed into one variable. These cut-off criteria were not so strict as to leave out all of the extreme scores, but stricter cut-off criteria would leave out important patient data, as most of the outliers were in the MCI-patient group and could therefore be considered valuable data. For recruitment procedures, inclusion and exclusion criteria, informed consents, ethical approval, DNA extraction and genotyping, see study 1.

5.2.3 Statistical Analysis

To get an account of the effect of normal aging, and MCI on different match measures, participants were divided into three subgroups: young control (YC): 19 – 45 years, N = 89 for match analysis, N = 91 for non-match analysis, old control (OC): 46 – 81 years, N = 219 for match analysis, N = 216 for non-match analysis, and MCI-group: 46 – 77 years, N = 45 for match analysis, N = 47 for non-match analysis. Participants were also splittet according to their genotype, leaving six groups; YC÷ε4 (N=57/59), YC+ε4 (N=32/32), OC÷ε4 (N=137/137), OC+ε4 (N=82/79), MCI÷ε4 (N=27/27), MCI+ε4 (N=18/20).

Mean accuracy response rate for target dot location was the measure of interest, and submitted for each condition in omnibus, repeated measures ANOVAs. Memory Load (one, two, or three target dots) and Target Distance (match, non-match close distance, non-match medium distance, non-match long distance) were within-subject factors, but because previous studies had found *APOE* effects when analyzing match conditions separate from non-match condition (Greenwood, Lambert, et al., 2005), the same separate omnibus ANOVA procedure for match trials and non-match trials was adopted. Thus Memory Load (3) and Target Distance (1 level for match-analysis, 3 levels for non-match analysis) were submitted as within-subject factors, and Group (YC, OC, MCI) and *APOE* (non-carriers , ε4-carriers) as between subject factors in two different omnibus ANOVAs.

A follow-up omnibus ANOVA for healthy age groups was conducted for both match and non-match trials, to get more detailed information about normal age related decline, and to check for possible *APOE* modulation in healthy age group. This procedure excluded the MCI group, and applied the same 50% cut-off score criteria. The remaining 314 participant were divided in three subgroups (Young Age (YA): 22.1 – 47.8 years, N=103, Middle Age (MA): 48.2 – 63.07 years, N=104, Old Age (OA): 63.21 – 81 years, N=100). The distribution of participants in normal age and *APOE* groups were as following: YA÷ε4 (N=66), YA+ε4 (N=37), MA÷ε4 (N=69), MA+ε4 (N=35), OA÷ε4 (N=61), OA+ε4 (N=39).

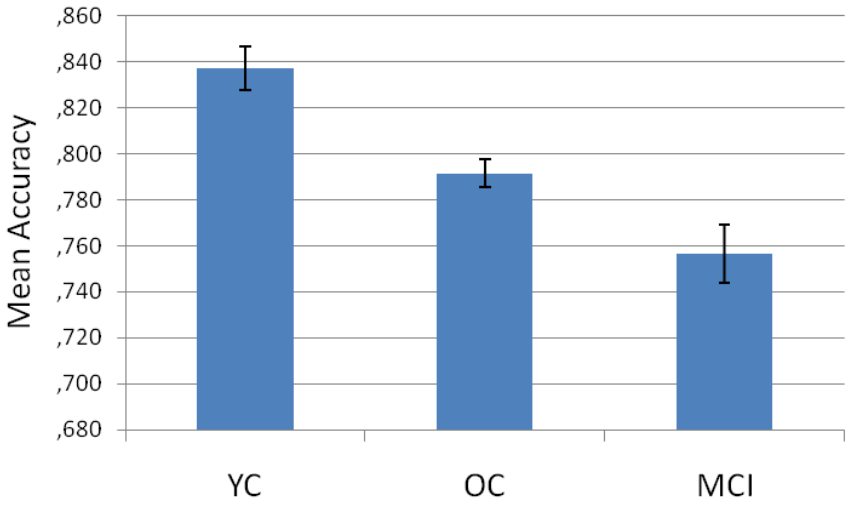
Also in this analysis, we did follow up omnibus repeated measure ANCOVAs with gender as a covariate (male = 236, female = 128) for both match and non-match trials, to control for possible biases related to gender distribution.

5.3 Results

Match trials. Omnibus ANOVA on match trials revealed a rather strong main effect of Memory Load, $F(2,347) = 157.37$, $p < .0005$, $\eta^2_p = .312$, indicating that when memory load increased, accuracy declined (.88 for one dot, .76 for two dots, .75 for three dots). This pattern was the same for all participants under all conditions, as no interactions with any of the between-subject factors were revealed. A main effect of Group was only marginal significant ($p = 0.79$), and no effects of *APOE* were found.

Non-match trials. The analysis revealed a main effect of Group, $F(2,358) = 14.73$, $p < .0005$, $\eta^2_p = .078$, indicating that accuracy rate declined with age, and due to MCI. YC had the highest correct responses rate (M = .83), MCI the lowest correct response rate (M = .75) and OC an intermediate value (M = .79), see figure 4.1. *APOE* was not involved in any of the non-match conditions, as no main or interaction effects with *APOE* were found.

Figure 4.1 Main effect Group on non-match trials



The analysis showed a main effect of Memory Load, $F(2,716) = 155.27$, $p < .0005$, $\eta^2_p = .309$, accuracy being highest for 1 dot condition (M = .85) lowest for three dot condition (M = .75) and in between value found in two dots condition (M = .79). A strong main effect of Target Distance was also found, $F(2,716) = 1322.3$, $p < .0005$, $\eta^2_p = .746$. Accuracy rate was highest for non-match long distance (M = .96), second highest for non-match medium distance (M = .85) and lowest for non-match close distance (M = .572). The effect of Distance was modulated by Load, as indicated by the Load × Distance interaction, $F(4,1432) = 50.764$, $p < .0005$, $\eta^2_p = .127$. Accuracy rates generally declined when Load increased except for long distance condition which stayed on a 96% accuracy rate. As memory load increased, accuracy declined for all other distance condition, and was lowest for non-match close distance in 3-dot load condition (M = .49). Thus, when memory load was high, and the distance between target and test dot was small, accuracy fell to a 50-50 chance level.

Group did modulate the effect of Distance, $F(4,716) = 8.647$, $p < .005$, $\eta^2_p = .047$, and was also involved in a two way interaction with Load, $F(4,716)$, $p = .023$, $\eta^2_p = .017$. Figure 4.2 shows that the decline in accuracy due to shorter test-target distance was proportional in the following manner: YC < OC < MCI, with MCI qualifying the largest effect. A similar steady decline in accuracy due to increase of Memory Load for all groups was found (see figure 4.3). Together, this shows that MCI diagnosis affects working memory measures of load demand and distance demand in a way that seems additive to the effect of normal aging. No significant effects of *APOE* or any other interactions were revealed in this analysis.

Figure 4.2 Distance × Group interaction

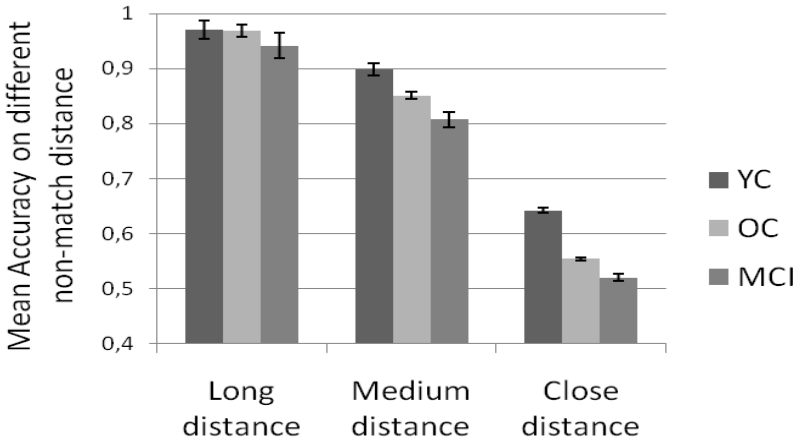
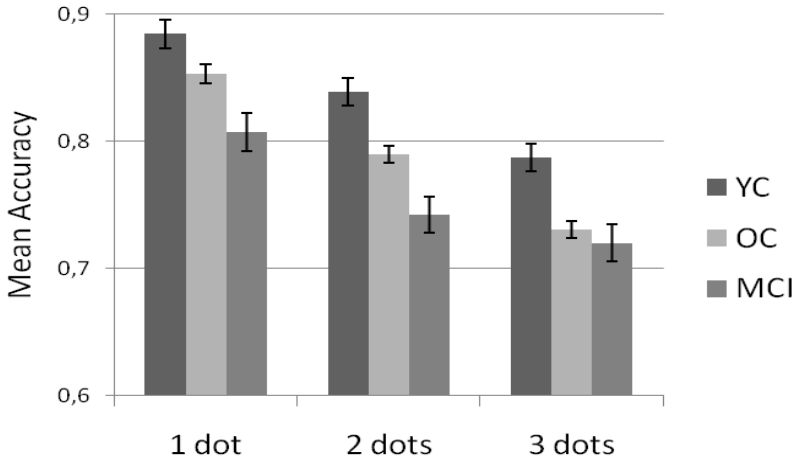
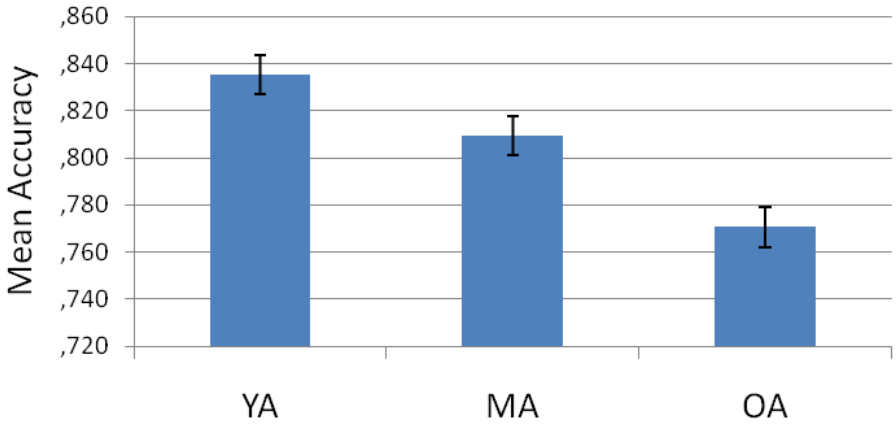


Figure 4.3 Load × Group interaction



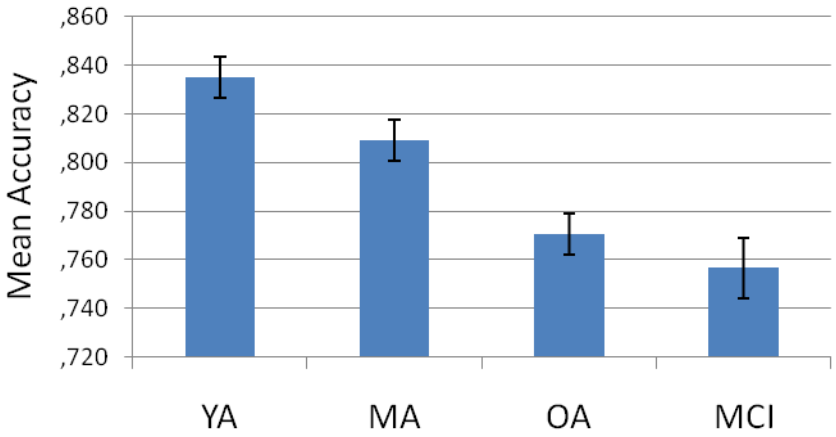
Healthy age analysis. Because of the steady decline YC < OC < MCI on both Load and Distance conditions, the development of accuracy scores in normal aging groups was examined in greater detail. This analysis revealed similar patterns as the former. On match trials an expected main effect of Load was found, $F(2,301) = 174.96$, $p < .0005$, $\eta^2_p = .368$, but no other effects were revealed. A main effect of Age Group was not significant ($p = .084$). On non-match trials, expected strong main effects of Load , $F(2,602) = 275.29$, $p < .0005$, $\eta^2_p = .747$, Distance, $F(2,602) = 1700.9$, $p < .0005$, $\eta^2_p = .85$, and Age Group were revealed , $F(2,301) = 15.148$, $p < .0005$, $\eta^2_p = .091$. Distance had the strongest effect and explained most of the total variation between groups (85%), accuracy being lowest for close distance non-match (M = .58), highest for long distance non-match (M = .969) and intermediate for medium distance non-match (M = .865). The main effect of Load exhibited a similar pattern to the former analysis, and figure 4.4 visualizes the main effect of Age Group, indicating a steady decline in accuracy due to age.

Figure 4.4 Main effect Age Group



The effect of Distance was modulated by Age Group, $F(4,602) = 11$, $p < .0005$, $\eta^2_p = .068$, showing that only the oldest age group fell to a chance level on close non-match distance condition. The effect of Distance was also modulated by Load, $F(4,1204) = 83$, $p < .0005$ $\eta^2_p = .216$. Load was modulated by Age Group, $F(4,602) = 2.634$, $p = .039$, $\eta^2_p = .017$, and the three-way interaction Distance × Load × Age Group, $F(8,1204) = 2.585$, $p = .018$, $\eta^2_p = .017$, indicated that the age effect on Distance was further modulated by Load, but no eminent pattern could be seen. No interactions with *APOE* were found in any of the possible interactions. Figure 4.5 summarizes the main effects of four healthy age groups and MCI.

Figure 4.5 Mean Accuracy for all groups



Gender covariate follow up. On match trials, gender was not involved (p's > .819). On non-match trails, gender interacted with Distance, $F(2,720) = 4.287$, $p = .026$, $\eta^2_p = .012$, indicating that accuracy rate for men fell more rapid due to shortening of distance than women. However, overall pattern of response did not alter much due to gender covariate involvement.

5.4 Discussion

As expected, results showed that accuracy declined due to load increase for all groups. The results also found an expected decline in accuracy when distance between cue and target on non-match conditions became smaller. Distance and Load also interacted, indicating that the highest demand situation (3 dots, non-match close distance) was difficult for all groups. When demand on both dimensions was maximized, performance declined to a chance level for all groups.

Because this experiment did not involve any manipulations that can be associated with activation of the attentional reorienting system, we did not expect to find specific interaction effects between MCI and *APOE*+ε4 on any of these measures. A main effect of Group was predicted, leading to an additive effect of MCI. It was found that Group did not affect match conditions, but a linear decline in non-match conditions were found for both Distance and Load on non-match conditions. When comparing overall accuracy response rates in healthy age control groups with MCI accuracy rate, a clear pattern of steady decline due to age and MCI was indicated (see figure 4.5). Thus, when load and resolution demands were manipulated, visuospatial working memory performance fell due to age, and MCI. The pattern of decline between healthy control groups and the MCI that was proportional, indicating a quantitatively difference. *APOE* was not involved in healthy age groups or in the MCI group. This indicates that pathological aging factor may reflect an acceleration of normal aging on visuospatial working memory performances, a pattern consistent with our prediction, as manipulations in the current experiment are not believed to activate the attentional reorienting system.

Based on previous findings, modulations of *APOE* were predicted, especially in the healthy control group. Findings in the current experiment contradicted studies that have found *APOE* modulations in healthy individuals on different working memory tasks like response inhibition (Reinvang, Winjevoll, et al., 2010) and more executive components of working memory (Rosen, Bergeson, Putnam, Harwell, & Sunderland, 2002). A previous study by Greenwood et al. (2005) also found subtle *APOE* modulations using the same visuospatial working memory paradigm as the one used in the current study. As mentioned in the methodology section, the separate match vs. non-match analysis were based on Greenwood et al.s (2005) procedures. They analyzed match and non-match trials separately, and found that

accuracy scores of homozygote ε4 carrier were significantly lower than non-carriers in three dot load condition in match conditions. Greenwood et al. (2005) tested participants on other measures as well, and found that healthy middle-aged *APOE*ε4-carriers exhibited deficits on both visuospatial attentional orienting (similar to the current experiment 1) and tasks where spatial location working memory and attention interacted, but point out that *APOE* affected brain areas modulating working memory less than it affected brain areas modulating visuospatial attention (Greenwood, Lambert, et al., 2005).

Why were no *APOE* modulations found in the current study? Some of the inconsistency between results in Experiment 1, 2 and 3 may be because different neurophysiologic systems are involved when attentional reorienting and visuospatial working memory are measured. Previous studies have indicate that the cholinergic system modulates attention, and noradrenergic and dopaminergic system modulated functions of working memory (Greenwood, et al., 2008). In the current experiment, working memory was measured on two visuospatial dimensions with different types of demand (load, distance). It may be that these manipulations are not sensitive to attentional processes, and this may in turn explain some of the missing *APOE* modulation. It has been proposed that *APOE* modulations are more consistent on integrity of the attentional system, whereas the integrity of working memory is less affected by the inheritance of an ε4 allele (Greenwood, Lambert, et al., 2005). Results from Greenwood et al. (2005) indicate that the ability to retain memory for location was reduced for the homozygote ε4-carrier in a much more subtle way than in measures of attentional reorienting. Further, as areas of the parietal lobe modulate attentional processes (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000), and AD is a disease associated with insults in the medial temporal and parietal lobe (Possin, 2010), and because *APOE* may be involved with cholinergic systems integrity declines with age (Reinvang, Lundervold, Wehling, Rootwelt, & Espeseth, 2010), one may assume lower effects of *APOE* on tests where attentional demands are low. However, the relationship between *APOE* and the cholinergic system is not yet well understood (Parasuraman, et al., 2002).

Another possible explanation why no *APOE* effects were found similar to Greenwood et al.s (2005) findings, may be due to different recruitment procedures, the fact that *APOE* interacts with many other factors before affecting cognition (Mahley, 2006; Parasuraman, et al., 2002; Reinvang, Lundervold, et al., 2010), but also the fact that the working memory stimuli paradigm measured accuracy response rate, while the visuospatial attention stimuli

paradigm measured reaction time. Maybe processing speed measures in experiment 1 & 2 are more sensitive to genetic modulations than accuracy measures? Further, the third experiment was difficult (some outliers accuracy scores near zero), and because these outliers were excluded, one may ask if this excluded the effects of *APOE* as well. *APOE* effects in the former experiments were found in the MCI group, and used as an indication of increased risk for AD. The MCI+ε4 groups were small, N = 27 in experiment 1, N = 21 in experiment 2, and N = 18 on match-trials in the current experiment. Maybe the low scores of the excluded patients were due to genuine effects of *APOE*? However, a final effort to explain the absence of an *APOE* × MCI interaction is consistent with our prediction; i.e. measures in this experiment did not activate the attentional reorienting system.

6 General discussion

The aim of this thesis was to examine how age, MCI and *APOE* influenced age-related decline in cognitive control functions. It was believed that specific measures of cognitive control were sensitive to distinguish incipient AD-development from normal aging processes. In terms of current methodology, it was hypothesized that interactive effects of MCI and *APOE*ε4 would lead to non-additive response patterns only on measures of the attentional reorienting system.

The results of this study gave evidence to support this hypothesis, as additive effects of MCI and no *APOE* modulations were found on tests not believed to activate the attentional reorienting system, i.e. all psychometric test scores (study 1), measures of visuospatial working memory (experiment 3), and performance on goal maintenance tasks following a valid cue (valid arrow in experiment 1 & AX trials in experiment 2) On these measures MCI accelerated the effect of normal aging in a quantitative way, a pattern consistent with the *unitary factor framework* that claims only one underlying factor contributing to pathological and normal aging, and that functional impairments associated with dementia reflects an acceleration of impairments that are found in normal aging (Buckner, 2004). Some of these results may also be understood in context of compensation and cognitive reserve theories. Compensation and cognitive reserve theories assume that alternative brain network recruitment, and cognitive strategies usage, may explain why neurological decline in the brain not fully can predict the variability in older peoples cognitive performance (Stern, 2002, 2003). The *underrecruitment hypothesis* claims that age-related decline is due to restriction in the availability of frontal resources, as these resources only will be elicited under certain conditions. (Logan, Sanders, Snyder, Morris, & Buckner, 2002). In conditions like high attentional demanding situations, older people benefit more from task strategy cues than younger people (Logan, et al., 2002). These external cues, or *environmental support*, contribute to improve the performances of older adults (Buckner, 2004; Logan, et al., 2002). The observed increase of Benefit in experiment 1, and unaffected AX trial scores in the MCI group in experiment 3 may indicate that older people used compensating strategies to meet with their deficits (general slowing being their deficit). Both a valid cue arrow, and an A before X can be seen as environmental support, as the cues were frequent and predictive.

Thus, one may assume that older individuals in the current study used *environmental support strategies* to compensate for age related decline in processing speed to improve performance.

On trials expected to activate the attentional reorienting system, current results suggest that MCI diagnosis in combination with *APOE*ε4 resulted in a non-additive effect. These measures were RTs after invalid arrow cue in the visuospatial reorienting task, and RTs after BX trials in the contextual updating task. Specifically, our results showed a "sudden" increase in Cost RT and BX RT in the MCI+ε4 group only. These patterns of response were interpreted as non-additive, because they indicated something different from an additive increase of age-related decline. The MCI÷ε4 group exhibited such an additive decline on these measures, but not the MCI+ε4 group. Non-additive response patterns of MCI+ε4 are consistent with the *multiple factor framework* claiming that different factors target different brain regions in pathology and normal aging, thus leading to different pattern of impairment (Buckner, 2004). According to Buckner (2004) medial-temporal areas are typically affected by AD-processes, whereas frontal-stratial areas are typically affected by normal aging processes. However, this does not mean that both areas can't be affected at the same time (Buckner, 2004). Buckner (2004) claims that processes leading to normal and pathological aging are in principal different processes, but may easily occur together, leading to severe cognitive decline. Can one assumed that the MCI+ε4 group is affected by both normal age-related and pathological aging processes? Are they more affected by pathological aging processes than the MCI÷ε4 group? Our results are consistent with the general believe that *APOE*ε4 increases the risk for AD-development in people with MCI (Wang, et al., 2010), and may thus indicate that areas of both dorsal and ventral frontoparietal regions are affected in the prodromal AD-development. The next section will argue that measures of invalid arrow cues and BX-trials are sensitive to impairments in the attentional reorienting system by describing how BX-trials and invalid cues activate the same underlying neurological circuits, before turning to evidence supporting the idea that aspects of the attentional reorienting system are specifically impaired in early AD.

6.1.1 Are measures of invalid arrow cues and BX-trials sensitive to impairments in the Attentional Reorienting System?

Neuroimaging studies indicate that the dorsal network is a control mechanism during ongoing behavior that send out top-down information to bias appropriate stimuli features and

location of stimuli (Corbetta, et al., 2008). The ventral frontoparietal network is independent of the dorsal network, but breaks the circuit and interrupts dorsal regions when a salient or behaviorally relevant stimuli outside the site of attention is detected and requires response (Corbetta, et al., 2008). Thus, reorienting of attention may in a neurophysiologic sense be understood in terms of the effectiveness of the ventral network output on interrupting ongoing activity in the dorsal network. But, how can one argue that invalid arrow cues and BX-trials will elicit this interaction between ventral and dorsal frontoparietal networks?

In the first experiment, the target letter was the stimuli that required action. To be able to respond to the target letter after an invalid cue, the person had to reorient his/her attention from the one side of the visual field to the other (Posner, 1980). Because most cues were valid, one may expect that a frequent valid arrow engages the dorsal network to pay attention on one side of the visual field. When however the target letter appeared on the other side, one may expect the ventral system to disrupt the dorsal network, and attention must be reoriented to the other side of the visual field. It can be assume that similar process are engaged in the AX-CPT task, even though this is a non-spatial task. Participants are required to reorient their attention internally, and respond according to context information (to respond to X only after an A). A valid AX trial is the most frequent trial and will biasing attention towards a specific response pattern. On BX trials, the B cue will bias the participants response to expect a non-X, thus probably engaging the dorsal network. When however the letter X appears, the participant must reorient attention to context information and make the correct response. Thus, one may assume that the letter X after B is an unexpected, but behaviorally relevant target that will activate the ventral network and break the ongoing circuit in the dorsal network.

As mentioned above, there is converging evidence from neuroimaging studies that both the dorsal system and the ventral systems interact when attention is reoriented by a novel and behaviorally relevant stimuli (Corbetta, et al., 2008). This has been replicated in many studies, for instance a fMRI study found activation of the ventral attention system in a spatial cueing paradigm based on Posners (1980), when both horizontal and vertical axes were implemented as directions of orienting, indicating that the ventral network is not limited to horizontal orienting tasks (Macaluso & Patria, 2007). Also in "signal-driven reorienting", that is when behaviorally irrelevant objects that share features with the relevant target, as in the oddball paradigm, the ventral system is involved (Espeseth, et al., in press). Other ventral

and dorsal reorienting network recruitments are described, for instance the temporoparietal juncion (TPJ), and the basal ganglia + frontal insula areas that are respectively recruited when attention shifts occurred from spatially, or when attentional reorienting occurred unexpected (Shulman et al., 2009). Studies on the AX-CPT task have found that the prefrontal cortex (PFC), and dopamine projections into the PFC are involved in a fMRI study involving 41 healthy adults ranging from age 18 – 83 (Braver & Barch, 2002) On visuospatial reorienting, the cholinergic system is believed to be involved (Parasuraman, et al., 2002). Inferior parts of the parietal cortex are in a fMRI study found to be involved in the disengagement of visuospatial attention (Corbetta, et al., 2000), and insults in the parietal cortex are also found to impair disengagement of visuospatial attention (Posner, et al., 1984). Further, the cholinergic system integrity seems to be important for an effective parietal mediation of the attentional tasks (Everitt & Robbins, 1997), and age associated decline in top-down attentional function may be due to deregulations and decline in the integrity of the cholinergic system (Sarter & Bruno, 2004). Also, a PET study measuring acetylcholinesterase activity in different cortical regions found a significant reduction of this activity in the parietal cortex in AD patients when compared with healthy control (Iyo et al., 1997).

Evidence supporting the idea of the ventral network as a protective filter in distinguishing relevant from non-relevant stimuli come from neuroimaging studies where internally and externally directed processes are examined. Internally directed processing, referred to as the *default system* is activated when no environmental stimuli require attention (Raichle & Snyder, 2007). The default system is believed to be mediated by similar areas as the dorsal attentional network (Corbetta, et al., 2008), i.e. medialfrontal, temporoparietal areas and areas around the posterior cingulate cortex (Raichle & Snyder, 2007; Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008) One hypothesis describes the default network as functional opposite of the dorsal attention network which directs attention towards environmental perception and action (Corbetta, et al., 2008), and is activated/deactivated by the absence/presence of external cues (Raichle & Snyder, 2007). As these dorsal attention system and the default system are believed to interact, reorienting is described as a process where the ventral frontoparietal network initiate a switch between internal and external systems. In this context the ventral network is believed to filter out which stimuli one should response to. An impairment in this system may lead to involuntarily reorienting between internal and external systems, for instance to reorient toward the environment when one is acquired to engage in self-referential thoughts (Corbetta, et al., 2008). Consistent with this

view, a suboptimal ventral network function will cause decline in attentional reorienting function. Results in the current study revealed a non-additive decline in the attentional reorienting function in the MCI+ε4 group only. There is reason to believe that people with early AD have functional impairments associated with ventral and the dorsal networks. For instance, several studies have indicated that the default system is impaired in people with MCI and further in people with AD, probably because of amyloid plaque deposits (Buckner, Andrews-Hanna, & Schacter, 2008; Buckner et al., 2005; Greicius, Srivastava, Reiss, & Menon, 2004; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005). Parasuraman et al. (1992) found specific AD-related impairments on invalid arrow cues, while Braver et al. (2005) found AD-related impairments on BX-trials. Taken together, this indicates that the observed decline in the MCI+ε4 group may reflect deficits in the ventral and dorsal frontoparietal networks, leading to the conclusion that the cued discrimination task and AX-CPT are behavioral assays that, in context of this study and its limitations, may be used to detect preclinical AD-development. The next question is if the attentional reorienting system may be understood as a possible endophenotype candidate linking *APOE* to AD?

6.1.2 The Attentional Reorienting System as an Endophenotype for Alzheimer's Disease?

Endophenotyping is used as a strategy to track effects of genetic variability on different mediating neuronal mechanisms (phenotypes), that link the gap between DNA sequence and pathology (Meyer-Lindenberg & Weinberger, 2006). Phenotypic parameters can ranging from molecular effects, neurobiochemistry, endocrinological, neuroanatomical, electrophysiology, to neuropsychological behavioral effects (Espeseth, et al., in press; Meyer-Lindenberg & Weinberger, 2006). Gottesman and Gould (2003) proposed several criteria for an endophenotype. An endophenotype has to be associated with illness in the population, to be heritable, and to be state independent (Gottesman & Gould, 2003). Further, as the endophenotype has to be associated with illness, Gottesman and Gould (2003) also claim that it has occur at higher rates in non-affected family members (for instant siblings of the affected family member) than in the general population. But there are few endophenotypes that actually fulfill all criteria, and the more behaviorally the phenotype, the smaller will the expected effect of a gene be (Meyer-Lindenberg & Weinberger, 2006). As we propose a neuropsychological endophenotype, one may not expect great genetic effects on the attentional reorienting system. In the current study, results on attentional reorienting measures

that involved MCI and *APOE* found partial eta squared's (η^2_p) between .001 (for Cost RTs) and .027 (for Condition-RTs), thus explaining between .1 – 2.7 % of total variability on these measures. This is generally considered as small effect sizes. For *APOE* main effects partial eta squared's were between .007 (for Cost Effect) and .012 (for Condition). However, one may argue that standard of the first criteria are met (the illness criteria), as attentional reorienting selectively was impaired for individuals at high risk for AD-development. To meet standards of the last criteria, one should include performance of different family members in the MCI+ε4 group to see if they have a more similar attentional reorienting impairment compared to the general population. This was not part of the current design. Besides, there does not exist standardized scores (as in a psychometric test) for measures of the attentional reorienting system. However, if one assumes attentional reorienting impairments is to be heritable, effects of *APOE*ε4 are only expected in people who are at risk for developing AD. We found initial evidence for this as normal age group performance were not impaired or affected by *APOE*. But, to meet full standard of heritability, twin/adoption studies should be conducted. Meyer-Lindenberg & Weinberger (2006) mention another criteria specific for a behavioral endophenotype is that the chosen behavioral assay must activate neural circuits that are plausibly translating genetic protein expressions to behavior. As mentioned above, neuroimaging, and neuropsychological studies support the view that an invalid arrow and BX trials activate ventral and dorsal frontoparietal networks. Taken together, there may be enough evidence to consider the attentional reorienting function as a candidate for *APOE*-AD endophenotype.

6.1.3 Limitations

Several limitations in this study may however affect the presented conclusion. For instance, the current study's clinical focus did not distinguish between AD and other possible forms of dementia that people in the MCI group may develop. Thus, one can not exclude the possibility that pathological processes leading to other forms of dementia affected performance in the MCI+ε4 group, even though AD is most prevalent dementia disease (Fratiglioni et al., 1991), and *APOE* generally is believed to be a risk gene for AD (Mahley, 2006). Second, the MCI diagnosis is a highly heterogeneous diagnosis, ranging from subjective complaints to accumulation of gross functional and structural impairments (Grambaite, et al., 2011; Grambaite et al., 2010; Petersen, et al., 2001), and some MCI-patients may remain stable(sMCI), and not develop AD (Vannini, et al., 2007). Thus an

unified group performance in the MCI group is unlikely to be expected. Also, it is known that pathological changes associated with amyloid deposits and neurofibrillary tangle appear early in development of AD (Braak & Braak, 1991), long before neuropsychological functions are affected (Parasuraman, et al., 2002), and we simply don't not know if people in our the old control group and MCI group overlapped according to neuropathological burden development in the brain. Thus, the clear distinction the current study design made between normal and pathological aging groups may in fact be unclear and mashed, and one cannot exclude the possibility that some of the 414 "healthy" participants in the OC group may be in a preclinical AD phase. Thus, if *APOE* modulation on attentional reorienting is to be understood as a preclinical AD endophenotype, one would expect to find *APOE* effect in the OC group as well.

Other limitations are concerned with the studies cross sectional design. A longitudinal design would give more information about possible cohort effects on these measures. Also, the modulation path between *APOE* and cholinergic network integrity are not fully understood, and further molecular genetic studies are needed to determine underlying mechanisms for how protein products of *APOE* polymorphisms modulate cholinergic transmissions to the posterior parietal cortex (Parasuraman, et al., 2002), and how the attentional reorienting system in involved in this context. Small et al. (2004) claim that when analyzing the effect of *APOE* on cognitive performance, several factors may cause inconsistent results. For instance the fact that the base rate of the *APOE*ε4-allele is small (14%) in comparison with *APOE*ε3 (78%) and *APOE*ε2-alleles (8%), may contribute to a lack of *APOE* effect on different cognitive performance (Small, et al., 2004). In the first experiment 27 participants belonged to the MCI+ε4 group, and in the second experiment the number of participants in the MCI+ε4 group was 21. This small sample size may exaggerate the effect of pathological aging. Also, as mentioned before, the ε4-allele increases the risk for developing AD, but the potency of this risk declines after a certain age (Breitner, et al., 1999). *APOE* seem to affect cognitive performance differently in different time of age (Mondadori, et al., 2007; Turic, et al., 2001).

In sum, even though we found evidence that measures of the attentional reorienting system were specifically impaired in the AD-high risk group (MCI+ε4), there are limitations to the generality of these findings.

6.2 Summary

The current study investigated the effects of normal aging, MCI and modulations of *APOE* on different measures of cognitive control, as cognitive control functions were believed to be sensitive for early AD-detection. Participants were tested on a wide specter of attentional and executive working memory control functions, measuring response on different distracter manipulations, context information manipulation, spatial resolution and load manipulations, using reaction time and accuracy rates, spatial and non-spatial measures, visual and auditory stimuli. We predicted to find non-additive effects on measures that activate the attentional reorienting system, and found support for this hypothesis, as only RTs after invalid arrow cues in experiment 1, and BX trials in experiment 2 involved an interaction between MCI and *APOE*ε4. Further, these interactions resulted in a qualitative difference between the MCI+ε4 group and age-matched control, indicating that these measures may be sensitive for prodromal AD-development. On measures of visuospatial working memory and psychometric tests, no effects of *APOE* were found, and patients with MCI and age-matched control group differed only quantitatively, indicating MCI accelerated functional decline associated with normal aging in this measure. Because BX trials and invalid arrow cue involved unexpected but behaviorally relevant targets, it was claimed that these measures are aspects of the same function which involves both dorsal and ventral frontoparietal networks, as described by Corbetta et al. (2008). Possibilities to view the attentional reorienting system as a candidate for a neuropsychological endophenotype being an intermediate step in the *APOE*-AD association were discussed according to criteria for endophenotypes. Finally, several limitations with this study were presented, like the absence of longitudinal follow up analysis, a possible inclusion of pre-clinical people with dementia in the control group, heterogeneousity in the MCI group, or small sample size in some analysis.

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